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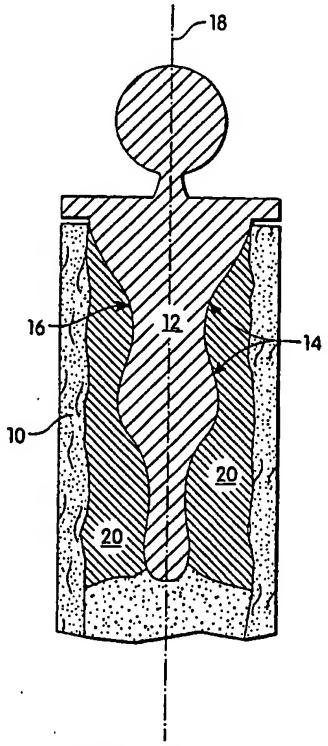

(57) Abstract

A prosthetic device comprising a prosthesis coated with substantially pure osteogenic protein is disclosed. A method for biologically fixing prosthetic devices *in vivo* is also disclosed. In this method, a prosthesis is implanted in an individual in contact with a substantially pure osteogenic protein, enhancing the strength of the bond between the prosthesis and the existing bone at the joining site.

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PROSTHETIC DEVICES HAVING ENHANCED OSTEOGENIC PROPERTIES

Reference to Related Applications

This application is a continuation-in-part of copending U.S. application Serial No. 07/841,646, filed 2/21/92, which is a continuation-in-part of U.S. Application Serial Nos. : 1) 07/827,052, filed January 28,1992, a divisional of USSN 07/179,406, filed April 8, 1988, now US 4,968,590; 2) 07/579,865, filed September 7, 1990, a divisional of USSN 07/179,406; 3) 07/621,849, filed December 4, 1990, a divisional of USSN 07/232,630, filed August 15, 1988, now abandoned, that was a continuation-in-part of 07/179,406; 4) 07/621,988, filed December 4, 1990, a divisional of 07/315,342 filed February 23, 1989, now US 5,011,691 and which is a continuation-in-part of 07/232,630; 5) 07/810,560, filed December 20, 1991, a continuation of 07/660,162, filed February 22, 1991, now abandoned, that was a continuation of 07/422,699, filed October 17, 1989, now abandoned, that was a continuation-in-part of 07/315,342; 6) 07/569,920, filed August 20, 1990, now abandoned, that was a continuation-in-part of 07/422,699 and 07/483,913, which is continuation-in-part of 07/422,613, filed October 17, 1989, now US 4,975,526 and which is a continuation-in-part of 07/315,342; 7) 07/600,024, filed October 18, 1990, a continuation-in-part of 07/569,920; 8) 07/599,543, filed October 18, 1990, a continuation-in-part of 07/569,920; 9) 07/616,374, filed November 21, 1990, a divisional of 07/422,613; and 10) 07/483,913, filed February 22, 1990.

Background of the Invention

Regeneration of skeletal tissues is thought to be regulated by specific protein factors that are naturally present within bone matrix. When a bone is damaged, these factors stimulate cells to form new cartilage and bone tissue which replaces or repairs lost or damaged bone. Regeneration of bone is particularly important where prosthetic implants are used without bonding cement to replace diseased bone, as in hip replacement. In these cases, formation of a tight bond between the prosthesis and the existing bone is very important, and successful function depends on the interaction between the implant and the bone tissue at the interface.

Bone healing can be stimulated by one or more osteogenic proteins which can induce a developmental cascade of cellular events resulting in endochondral bone formation. Proteins stimulating bone growth have been referred to in the literature as bone morphogenic proteins, bone inductive proteins, osteogenic proteins, osteogenin or osteoinductive proteins.

U.S. 4,968,590 (November 6, 1990) discloses the purification of "substantially pure" osteogenic protein from bone, capable of inducing endochondral bone formation in a mammal when implanted in the mammal in association with a matrix, and having a half maximum activity of at least about 25 to 50 nanograms per 25 milligrams of implanted matrix. Higher activity subsequently has been shown for this protein, e.g., 0.8-1.0 ng of osteogenic protein per mg of implant matrix, as disclosed in U.S. Patent 5,011,691. This patent also disclosed a consensus DNA sequence probe useful for identifying genes encoding osteogenic proteins, and a number of human genes encoding osteogenic proteins identified using the consensus probe, including a previously unidentified gene referred to therein as "OP1" (osteogenic protein-1). The consensus probe also identified DNA

sequences corresponding to sequences termed BMP-2 Class I and Class II ("BMP2" and "BMP4" respectively) and BMP3 in International Appl. No. PCT/US87/01537. The osteogenic proteins encoded by these sequences are referred to herein as "CBMP2A," "CBMP2B", and "CBMP3", respectively. U.S. 5,011,691 also defined a consensus "active region" required for osteogenic activity and described several novel biosynthetic constructs using this consensus sequence which were capable of inducing cartilage or bone formation in a mammal in association with a matrix.

These and other researchers have stated that successful implantation of the osteogenic factors for endochondral bone formation requires that the proteins be associated with a suitable carrier material or matrix which maintains the proteins at the site of application. Bone collagen particles which remain after demineralization, guanidine extraction and delipidation of pulverized bone have been used for this purpose. Many osteoinductive proteins are useful cross-species. However, demineralized, delipidated, guanidine-extracted xenogenic collagen matrices typically have inhibited bone induction in vivo. Sampath and Reddi (1983) Proc. Natl. Acad. Sci. USA, 80: 6591-6594. Recently, however, Sampath et al. have described a method for treating demineralized guanidine-extracted bone powder to create a matrix useful for xenogenic implants. See, U.S. 4,975,526 (December 4, 1990). Other useful matrix materials include for example, collagen; homopolymers or copolymers of glycolic acid, lactic acid, and butryic acid, including derivatives thereof; and ceramics, such as hydroxyapatite, tricalcium phosphate and other calcium phosphates. Combinations of these matrix materials also may be useful.

Orthopedic implants have traditionally been attached to natural bone using bone cement. More recently, cementless prostheses have been used, in which the portion of the prosthesis that contacts the natural bone is coated with a

porous material. M. Spector, J. Arthroplasty, 2(2):163-176 (1987); and Cook et al., Clin. Orthoped. and Rel. Res., 232: 225-243 (1988). Cementless fixation is preferred because biological fixation of the prosthesis is stronger when osseointegration is achieved. The porous coatings reportedly stimulate bone ingrowth resulting in enhanced biological fixation of the prosthesis. However, there are several problems with porous-coated prostheses. For example, careful prosthetic selection is required to obtain a close fit with the bone to ensure initial mechanical stabilization of the device, and surgical precision is required to ensure initial implant-bone contact to promote bone ingrowth. Porous coated implants have not resulted in bone ingrowth in some instances, for example, in porous coated tibial plateaus used in knee replacements. A prosthetic implant that results in significant bone ingrowth and forms a strong bond with the natural bone at the site of the join would be very valuable.

The current state of the art for the anchoring of embedded implants such as dental implants also is unsatisfactory. Typically, dental implant fixation first requires preparing a tooth socket in the jawbone of an individual for prosthesis implantation by allowing bone ingrowth into the socket void to fill in the socket. This preparatory step alone can take several months to complete. The prosthesis then is threaded into the new bone in the socket and new bone is allowed to regrow around the threaded portion of the implant embedded in the socket. The interval between tooth extraction and prosthetic restoration therefore can take up to eight months. In addition, threading the prosthesis into bone can damage the integrity of the bone. Prosthetic dental implants that can improve osseointegration and reduce the time and effort for fixation would be advantageous.

Summary of the Invention

The present invention relates to a method of enhancing the growth of bone at the site of implantation of a prosthesis to form a bond between the prosthesis and the existing bone. As used herein, a prosthesis is understood to describe the addition of an artificial part to supply a defect in the body. The method involves coating or otherwise contacting all or a portion of the prosthesis that will be in contact with bone with a substantially pure osteogenic protein. The prosthesis first may be coated with the osteogenic protein and then implanted in the individual at a site wherein the bone tissue and the surface of the prosthesis are maintained in close proximity for a time sufficient to permit enhanced bone tissue growth between the tissue and the implanted prosthesis. Alternatively, the site of implantation first may be treated with substantially pure osteogenic protein and the prosthesis then implanted at the treated site such that all or a portion of the prosthesis is in contact with the osteogenic protein at the site, and the prosthesis, the osteogenic protein and the existing bone tissue are maintained in close proximity to one another for a time sufficient to permit enhanced bone tissue growth between the tissue and the prosthesis. The osteogenic protein associated with the implanted prosthesis stimulates bone growth around the prosthesis and causes a stronger bond to form between the prosthesis and the existing bone than would form between the prosthesis and the bone in the absence of the protein.

In a preferred embodiment of the present method a prosthetic device, such as an artificial hip replacement device, e.g., a metallic device made from titanium, for example, is first coated with an osteogenic material which induces bone ingrowth. When the device is subsequently implanted into the individual, bone growth around the site of the implant is enhanced, causing a strong bond to form

between the implant and the existing bone. The present method results in enhanced biological fixation of the prosthesis in the body, which is particularly important for weight bearing prostheses. Prostheses defining a microporous surface structure are locked in place as bone formation occurs within the micropores. The metal or ceramic prosthesis may itself define such a structure, or the prosthesis may be coated to provide an adherent porous surface. Materials useful for this purpose include, for example, collagen, homopolymers of glycolic acid, lactic acid, and butyric acid, including derivatives thereof; and ceramics such as hydroxyapatite, tricalcium phosphate or other calcium phosphates. Combinations of these materials may be used. A substantially pure osteogenic protein is then bound to the uncoated or coated prosthesis. Alternatively, the osteogenic protein can be mixed with the coating material, and the mixture adhered onto the surface of the prosthesis.

In another embodiment of the present invention, osteogenic protein combined with a matrix material is packed into an orifice prepared to receive the prosthetic implant. The surface of the implant also may be coated with osteogenic protein, as described above. The implant has a shape defining one or more indentations to permit bone ingrowth. The indentations are preferably transverse to the longitudinal axis of the implant. In general, the longitudinal axis of the implant will be parallel to the longitudinal axis of the bone which has been treated to receive the implant. New bone grows into the indentations thereby filling them, integrates with the surface of the implant as described above, and integrates with existing bone. Thus, the prosthesis can be more tightly fixed into the orifice, and "latched" or held in place by bone growing into the indentations, and by osseointegration of new bone with the surface of the implant, both of which are stimulated by the osteogenic protein.

In a specific embodiment, a dental implant is used to replace missing teeth. The implant typically comprises a threaded portion which is fixed into the jawbone and a tooth portion configured to integrate with the rest of the patient's teeth. The implant is coated with osteogenic protein (with or without a matrix or carrier) and threaded or screwed into a tooth socket in the jawbone prepared to receive it (e.g., bone has been allowed to grow into and fill the socket void.) In a particularly preferred embodiment, the socket is prepared to receive the implant by packing the void with a bone growth composition composed of osteogenic protein dispersed in a suitable carrier material. The combination of osteogenic protein and carrier is referred to herein as an "osteogenic device." The osteogenic protein promotes osseointegration of the implant into the jawbone without first requiring bone growth to fill the socket, and without requiring that the prosthesis be threaded into existing bone, which may weaken the integrity of the the existing bone. Accordingly, the time interval between tooth extraction and prosthetic restoration is reduced significantly. It is anticipated that prosthetic restoration may be complete in as little time as one month. In addition, the ability of the osteogenic protein to promote osseointegration of the prosthesis will provide a superior anchor.

A prosthetic device coated with the above osteogenic protein also is the subject of the present invention. All or a portion of the device may be coated with the protein. Generally, only the portion of the device which will be in contact with the existing bone will be coated.

The present method and device results in enhanced biological fixation of the prosthesis. A strong bond is formed between the existing bone and the prosthesis, resulting in improved mechanical strength at the joining

site. Higher attachment strength means that the prosthesis will be more secure and permanent, and therefore will be more comfortable and durable for the patient.

Brief Description of the Drawing

The sole Figure of the drawing schematically depicts a cross-sectional view of a portion of a prosthesis implanted in a femur and illustrates the latching action of bone ingrowth in accordance with an embodiment of the invention.

Detailed Description of the Invention

The present invention relates to a method for enhancing osseointegration between a prosthesis and natural bone in an individual at the site of implantation of the prosthesis. The method involves providing a prosthesis to a site of implantation together with substantially pure osteogenic protein such that the osteogenic protein is in contact with all or a portion of the implanted prosthesis. The protein promotes osseointegration of the prosthesis and the bone, resulting in a strong bond having improved tensile strength.

Osteogenic proteins which are useful in the present invention are substantially pure osteogenically active dimeric proteins. As used herein "substantially pure" means substantially free of other contaminating proteins having no endochondral bone formation activity. The protein can be either natural-sourced protein derived from mammalian bone or recombinantly produced proteins, including biosynthetic constructs. The natural-sourced proteins are characterized by having a half maximum activity of at least 25 to 50 ng per 25 mg of demineralized protein extracted bone powder, as compared to rat demineralized bone powder.

The natural-sourced osteogenic protein in its mature, native form is a glycosylated dimer having an apparent molecular weight of about 30 kDa as determined by SDS-PAGE. When reduced, the 30 kDa protein gives rise to two glycosylated peptide subunits having apparent molecular weights of about 16 kDa and 18 kDa. In the reduced state, the protein has no detectable osteogenic activity. The unglycosylated protein, which also has osteogenic activity, has an apparent molecular weight of about 27 kDa. When reduced, the 27 kDa protein gives rise to two unglycosylated polypeptides having molecular weights of about 14 kDa to 16 kDa. The recombinantly-produced osteogenic protein describes a class of dimeric proteins capable of inducing endochondral bone formation in a mammal comprising a pair of

polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence of the biosynthetic constructs or COP-5 Or COP-7, (SEQ. ID NOS.3 and 4), such that said pair of polypeptide chains, when disulfide bonded to produce a dimeric species is capable of inducing endochondral bone formation in a mammal. As defined herein, "sufficiently duplicative" is understood to describe the class of proteins having endochondral bone activity as dimeric proteins implanted in a mammal in association with a matrix, each of the subunits having at least 60% amino acid sequence homology in the C-terminal cysteine-rich region with the sequence of OPS (residues 335 to 431, SEQ. ID No. 1). "Homology" is defined herein as amino acid sequence identity or conservative amino acid changes within the sequence, as defined by Dayoff, et al., Atlas of Protein Sequence and Structure; vol.5, Supp.3, pp.345-362, (M.O. Dayoff, ed. Nat'l Biomed. Research Fdn., Washington, D.C., 1979.) Useful sequences include those comprising the C-terminal sequences of DPP (from Drosophila), Vgl (from Xenopus), Vgr-1 (from mouse), the OP1 and OP2 proteins, the CBMP2, CBMP3, and CBMP4 proteins (see U.S. Pat. No. 5,011,691 and U.S. Application Serial No. 07/841,646 by Oppermann et al., filed February 21, 1992, the disclosures of both of which are hereby incorporated by reference, as well as the proteins referred to as BMP5 and BMP6 (see WO90/11366, PCT/US90/01630.) A number of these proteins also are described in WO88/00205, U.S. Patent No. 5,013,649 and WO91/18098. Table I provides a list of the preferred members of this family of osteogenic proteins.

TABLE I - OSTEOGENIC PROTEIN SEQUENCES

hOP1 - DNA sequence encoding human OP1 protein (Seq. ID No. 1 or 3). Also referred to in related applications as "OP1", "hOP-1" and "OP-1".

OP1 - Refers generically to the family of osteogenically active proteins produced by expression of part or all of the hOP1 gene. Also referred to in related applications as "OPI" and OP-1".

hOP1-PP - Amino acid sequence of human OP1 protein (prepro form), Seq. ID No. 1, residues 1-431. Also referred to in related applications as "OP1-PP" and "OPP".

OP1-18Ser - Amino acid sequence of mature human OP1 protein, Seq. ID No. 1, residues 293-431. N-terminal amino acid is serine. Originally identified as migrating at 18 kDa on SDS-PAGE in COS cells. Depending on protein glycosylation pattern in different host cells, also migrates at 23kDa, 19kDa and 17kDa on SDS-PAGE. Also referred to in related applications as "OP1-18".

OPS - Human OP1 protein species defining the conserved 6 cysteine skeleton in the active region (97 amino acids, Seq. ID No. 1, residues 335-431). "S" stands for "short".

OP7 - Human OP1 protein species defining the conserved 7 cysteine skeleton in the active region (102 amino acids, Seq. ID No. 1, residues 330-431).

OP1-16Ser - N-terminally truncated mature human OP1 protein species. (Seq. ID No. 1, residues 300-431). N-terminal amino acid is serine; protein migrates at 16kDa or 15kDa on

SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16S".

OP1-16Leu - N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 313-431. N-terminal amino acid is leucine; protein migrates at 16 or 15kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16L".

OP1-16Met - N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 315-431. N-terminal amino acid is methionine; protein migrates at 16 or 15kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16M".

OP1-16Ala - N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 316-431. N-terminal amino acid is alanine, protein migrates at 16 or 15 kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16A".

OP1-16Val - N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 318-431. N-terminal amino acid is valine; protein migrates at 16 or 15 kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16V".

mOP1 - DNA encoding mouse OP1 protein, Seq. ID No. 8. Also referred to in related applications as "mOP-1".

mOP1-PP - Prepro form of mouse protein, Seq. ID No. 8, residues 1-430. Also referred to in related applications as "mOP-1-PP".

mOP1-Ser - Mature mouse OP1 protein species (Seq. ID No. 8, residues 292-430). N-terminal amino acid is serine. Also referred to in related applications as "mOP1" and "mOP-1".

mOP2 - DNA encoding mouse OP2 protein, Seq. ID No. 12. Also referred to in related applications as "mOP-2".

mOP2-PP - Prepro form of mOP2 protein, Seq. ID No. 12, residues 1-399. Also referred to in related applications as "mOP-2-PP".

mOP2-Ala - Mature mouse OP2 protein, Seq. ID No. 12, residues 261-399. N-terminal amino acid in alanine. Also referred to in related applications as "mOP2" and "mOP-2".

hOP2 - DNA encoding human OP2 protein, Seq. ID No. 10. Also referred to in related applications as "hOP-2".

hOP2-PP - Prepro form of human OP2 protein, Seq. ID No. 10, res. 1-402). Also referred to in related applications as "hOP-2-PP".

hOP2-Ala - Possible mature human OP2 protein species: Seq. ID No. 10, residues 264-402. Also referred to in related applications as "hOP-2".

hOP2-Pro - Possible mature human OP2 protein species: Seq. ID No. 10, residues 267-402. N-terminal amino acid is proline. Also referred to in related applications as "hOP-2P".

hOP2-Arg - Possible mature human OP2 protein species: Seq. ID No. 10, res. 270-402. N-terminal amino acid is arginine. Also referred to in related applications as "hOP-2R".

hOP2-Ser - Possible mature human OP2 protein species: Seq. ID No. 10, res. 243-402. N-terminal amino acid is serine. Also referred to in related applications as "hOP-2S".

Vgr-1-fx C-terminal 102 amino acid residues of the murine "Vgr-1" protein (Seq. ID No. 7).

CBMP2A C-terminal 101 amino acid residues of the human BMP2A protein. (Residues 296-396 of Seq. ID No. 14).

CBMP2B C-terminal 101 amino acid residues of the human BMP2B protein. (Seq. ID No. 18).

BMP3 Mature human BMP3 (partial sequence, Seq. ID No. 16. See U.S. 5,011,691 for C-terminal 102 residues, "CBMP3.")

BMP5-fx C-terminal 102 amino acid residues of the human BMP5 protein. (Seq ID No. 20).

BMP6-fx	C-terminal 102 amino acid residues of the human BMP6 protein. (Seq ID No. 21).
COP5	Biosynthetic ostegenic 96 amino acid sequence (Seq. ID No. 3).
COP7	Biosynthetic osteogenic 96 amino acid sequence (Seq. ID No. 4).
DPP-fx	C-terminal 102 amino acid residues of the Drosophila "DPP" protein (Seq. ID No. 5).
Vgl-fx	C-terminal 102 amino acid residues of the Xenopus "Vgl" protein (Seq. ID No. 6).

The members of this family of proteins share a conserved six or seven cysteine skeleton in this region (e.g., the linear arrangement of these C-terminal cysteine residues is conserved in the different proteins.) See, for example, OPS, whose sequence defines the six cysteine skeleton, or OP7, a longer form of OP1, comprising 102 amino acids and whose sequence defines the seven cysteine skeleton.) In addition, the OP2 proteins contain an additional cysteine residue within this region.

This family of proteins includes longer forms of a given protein, as well as species and allelic variants and biosynthetic mutants, including addition and deletion mutants and variants, such as those which may alter the conserved C-terminal cysteine skeleton, provided that the alteration still allows the protein to form a dimeric species having a conformation capable of inducing bone formation in a mammal when implanted in the mammal in association with a matrix. In addition, the osteogenic proteins useful in devices of this invention may include forms having varying glycosylation patterns and varying

N-termini, may be naturally occurring or biosynthetically derived, and may be produced by expression of recombinant DNA in procaryotic or eucaryotic host cells. The proteins are active as a single species (e.g., as homodimers), or combined as a mixed species.

A particularly preferred embodiment of the proteins useful in the prosthetic devices of this invention includes proteins whose amino acid sequence in the cysteine-rich C-terminal domain has greater than 60% identity, and preferably greater than 65% identity with the amino acid sequence of OPS.

In another preferred aspect, the invention comprises osteogenic proteins comprising species of polypeptide chains having the generic amino acid sequence herein referred to as "OPX" which accommodates the homologies between the various identified species of the osteogenic OP1 and OP2 proteins, and which is described by the amino acid sequence of Sequence ID No. 22.

In still another preferred aspect, the invention comprises nucleic acids and the osteogenically active polypeptide chains encoded by these nucleic acids which hybridize to DNA or RNA sequences encoding the active region of OP1 or OP2 under stringent hybridization conditions. As used herein, stringent hybridization conditions are defined as hybridization in 40% formamide, 5 X SSPE, 5 X Denhardt's Solution, and 0.1% SDS at 37°C overnight, and washing in 0.1 X SSPE, 0.1% SDS at 50°C.

The invention further comprises nucleic acids and the osteogenically active polypeptide chains encoded by these nucleic acids which hybridize to the "pro" region of the OP1 or OP2 proteins under stringent hybridization conditions. As used herein, "osteogenically active polypeptide chains" is understood to mean those polypeptide chains which, when dimerized, produce a protein species having a conformation such that the pair of polypeptide chains is capable of

inducing endochondral bone formation in a mammal when implanted in a mammal in association with a matrix or carrier.

Given the foregoing amino acid and DNA sequence information, the level of skill in the art, and the disclosures of U.S. Patent 5,011,691 and published PCT specification US 89/01469, published October 19, 1989, the disclosures of which are incorporated herein by reference, various DNAs can be constructed which encode at least the active domain of an osteogenic protein useful in the devices of this invention, and various analogs thereof (including species and allelic variants and those containing genetically engineered mutations), as well as fusion proteins, truncated forms of the mature proteins, deletion and addition mutants, and similar constructs. Moreover, DNA hybridization probes can be constructed from fragments of any of these proteins, or designed de novo from the generic sequence. These probes then can be used to screen different genomic and cDNA libraries to identify additional osteogenic proteins useful in the prosthetic devices of this invention.

The DNAs can be produced by those skilled in the art using well known DNA manipulation techniques involving genomic and cDNA isolation, construction of synthetic DNA from synthesized oligonucleotides, and cassette mutagenesis techniques. 15-100mer oligonucleotides may be synthesized on a DNA synthesizer, and purified by polyacrylamide gel electrophoresis (PAGE) in Tris-Borate-EDTA buffer. The DNA then may be electroeluted from the gel. Overlapping oligomers may be phosphorylated by T4 polynucleotide kinase and ligated into larger blocks which may also be purified by PAGE.

The DNA from appropriately identified clones then can be isolated, subcloned (preferably into an expression vector), and sequenced. Plasmids containing sequences of interest then can be transfected into an appropriate host cell for

protein expression and further characterization. The host may be a procaryotic or eucaryotic cell since the former's inability to glycosylate protein will not destroy the protein's morphogenic activity. Useful host cells include E. coli, Saccharomyces, the insect/baculovirus cell system, myeloma cells, CHO cells and various other mammalian cells. The vectors additionally may encode various sequences to promote correct expression of the recombinant protein, including transcription promoter and termination sequences, enhancer sequences, preferred ribosome binding site sequences, preferred mRNA leader sequences, preferred signal sequences for protein secretion, and the like.

The DNA sequence encoding the gene of interest also may be manipulated to remove potentially inhibiting sequences or to minimize unwanted secondary structure formation. The recombinant osteogenic protein also may be expressed as a fusion protein. After being translated, the protein may be purified from the cells themselves or recovered from the culture medium. All biologically active protein forms comprise dimeric species joined by disulfide bonds or otherwise associated, produced by folding and oxidizing one or more of the various recombinant polypeptide chains within an appropriate eucaryotic cell or in vitro after expression of individual subunits. A detailed description of osteogenic proteins expressed from recombinant DNA in E. coli is disclosed in U.S. Serial No. 422,699 filed October 17, 1989, the disclosure of which is incorporated herein by reference. A detailed description of osteogenic proteins expressed from recombinant DNA in numerous different mammalian cells is disclosed in U.S. Serial No. 569,920 filed August 20, 1990, the disclosure of which is hereby incorporated by reference.

Alternatively, osteogenic polypeptide chains can be synthesized chemically using conventional peptide synthesis techniques well known to those having ordinary skill in the

art. For example, the proteins may be synthesized intact or in parts on a solid phase peptide synthesizer, using standard operating procedures. Completed chains then are deprotected and purified by HPLC (high pressure liquid chromatography). If the protein is synthesized in parts, the parts may be peptide bonded using standard methodologies to form the intact protein. In general, the manner in which the osteogenic proteins are made can be conventional and does not form a part of this invention.

The osteogenic proteins useful in the present invention are proteins which, when implanted in a mammalian body, induce the developmental cascade of endochondral bone formation including recruitment and proliferation of mesenchymal cells, differentiation of progenitor cells, cartilage formation, calcification of cartilage, vascular invasion, bone formation, remodeling and bone marrow differentiation. The osteopenic protein in contact with the present prostheses can induce the full developmental cascade of endochondral bone formation at the site of implantation essentially as it occurs in natural bone healing.

Prostheses which can be used with the present method include porous or non-porous orthopedic prostheses of the types well known in the art. Such prostheses are generally fabricated from rigid materials such as metals, including for example, stainless steel, titanium, molybdenum, cobalt, chromium and/or alloys or oxides of these metals. Such oxides typically comprise a thin, stable, adherent metal oxide surface coating. The prostheses are preferably formed from or coated with porous metals to permit infiltration of the bone, but non-porous materials also can be used. Porous metallic materials for use in prostheses are described, for example, by Spector in J. Arthroplasty, 2(2):163-176 (1987), and by Cook et al. in Clin. Orthoped. and Rel. Res., 232:225-243 (1988), the teachings of both of which are hereby incorporated herein by reference. Metallic

prostheses may be used for major bone or joint replacement and for repairing non-union fractures, for example, where the existing bone has been destroyed by disease or injury.

In a preferred embodiment of the present device and method, the prosthesis is coated with a material which enhances bone ingrowth and fixation, in addition to the protein. Materials which are useful for this purpose are biocompatible, and preferably in vivo biodegradable and non-immunogenic. Such materials include, for example, collagen, hydroxyapatite, homopolymers or copolymers of glycolic acid lactic acid, and butyric acid and derivatives thereof, tricalcium phosphate or other calcium phosphates, metal oxides, (e.g., titanium oxide), and demineralized, guanidine extracted bone.

The present coated prostheses are prepared by applying a solution of the protein, and optionally, hydroxylapatite or other material to all or a portion of the prosthesis. The protein can be applied by any convenient method, for example, by dipping, brushing, immersing, spraying or freeze-drying. Hydroxylapatite is preferably applied by a plasma spraying process. The protein is preferably applied by immersing the prostheses in a solution of the protein under conditions appropriate to induce binding or precipitation of the protein from solution onto the implant. The amount of protein which is applied to the implant should be a concentration sufficient to induce endochondral bone formation when the prosthesis is implanted in the recipient. Generally a concentration in the range of at least 5μg protein per 3.4cm^2 surface area is sufficient for this purpose. If hydroxylapatite or other carrier material is used, it is applied to the prosthesis in an amount required to form a coating of from about 15μ to about 60μ thick. A layer about 25μ thick of hydroxylapatite has been used to improve implant fixation, as shown in the exemplification.

In one aspect, the prosthesis comprises a device configured for insertion into an orifice prepared to receive the prosthesis. In this embodiment, as illustrated in the Figure, the interior of a bone 10 is hollowed out in preparation for insertion of the implant 12. The implant has a contoured surface design 14 defining plural indentations 16 to permit ingrowth of bone into the indentations. The indentations are preferably transverse to the longitudinal axis 18 of the implant. The contoured portion to be inserted in the orifice may be coated with osteogenic protein as described above. Osteogenic protein combined with a matrix material 20 is packed into the orifice with the prosthetic implant, thereby surrounding it. Stimulated by the osteogenic protein, new bone grows into the indentations 16 and becomes integrated with the surface of the implant 12 and with preexisting bone 10 as described above. Thus, the prosthesis is both mechanically and biologically fixed in place, and axial movement of the implant relative to the bone requires shearing of bone tissue. Matrix material 20 can be any of the materials described above for coating the prosthesis for enhancing bone growth and fixation, e.g., collagen, hydroxyapatite, homopolymers or copolymers of glycolic acid lactic acid, and butyric acid and derivatives thereof, tricalcium phosphate or other calcium phosphates, metal oxides and demineralized, guanidine extracted bone. Matrix materials for use with osteogenic proteins which can be used in the present embodiment are those described, for example, in U.S. Patent 5,011,691 and in copending U.S. patent application Serial No. 07/841,646 by Oppermann et al., filed February 21, 1992, the teachings of which are hereby incorporated by reference.

The prothesis illustrated in the Figure is particularly useful for dental and other implants where at last part of the prosthesis is to be embedded into bone tissue. Packing the orifice, e.g., tooth socket, with an "osteogenic

device," e.g., osteogenic protein in combination with a matrix material, provides a solid material in which to embed the prosthesis without requiring that the device be threaded into existing bone. Moreover, the osteogenic protein stimulates endochondral bone formation within the socket and into and around the implant, thereby obviating the previously required step of first allowing bone ingrowth into the socket in order to provide a suitable surface into which to implant the prosthesis. Accordingly, using the method and devices of the invention, strong fixation of an implanted prosthesis may be achieved in a fraction of the time previously required, significantly shortening the time interval between tooth extraction and prosthetic restoration. In addition, this treatment may expand the use of implant therapy and enhance success rates by eliminating a surgical procedure, reducing the amount of bone lost following tooth extraction, permitting the insertion of longer implants and minimizing prosthetic compromises necessitated by alveolar ridge resorption.

The invention will be further illustrated by the following Exemplification which is not intended to be limiting in any way.

EXEMPLIFICATION

Example 1

Metal Implant Fixation

Cylindrical implants 18mm in length and 5.95 $\pm$ 0.05mm in diameter were fabricated from spherical Co-Cr-Mo particles resulting in a pore size of 250-300μm and a volume porosity of 38-40%. A highly crystalline, high density and low porosity hydroxylapatite (HA) coating was applied by plasma spray process to one-half of the length of each of the implants. The coating thickness was 25 μm and did not alter the porous coating morphology.

In the initial study, three implants were treated with a partially purified bovine OP (bOP) preparation. The bOP was naturally sourced OP extracted from cortical bone and partially purified through the Sephacryl-300 HR step in the purification protocol as described in Sampath et al. (1990), J. Biol. Chem., 265: 13198-13205. 200µl aliquots of 4 M guanidine-HCl, 50 mM Tris-HCl, pH 7.0, containing approximately 80 µg bOP were added to each implant in an eppendorf tube. After overnight incubation at 4°C the protein was precipitated and the implant washed with 80% ethanol. The implants were subsequently freeze dried. Two implants without bOP served as the controls.

The implants were evaluated in one skeletally mature adult mongrel dog (3-5 years old, 20-25Kg weight) using the femoral transcortical model. Standard surgical techniques were used such that the animal received the five implants in one femur. At three weeks the dog was sacrificed and the femur removed.

The harvested femur was sectioned transverse to the long axis such that each implant was isolated. Each implant was sectioned in half to yield one HA-coated and one uncoated push-out sample. Interface attachment strength was determined using a specifically designed test fixture. The implants were pushed to failure with a MTS test machine at a displacement rate of 1.27 mm/minute. After testing, all samples were prepared for standard undecalcified histologic and microradiographic analyses. The sections (4 sections from each implant) were qualitatively examined for the type and quality of tissue ingrowth, and quantitatively evaluated for % bone ingrowth with a computerized image analysis system. The mechanical and quantitative histological data is shown in Table II.

TABLE II
METAL IMPLANTS - bOP

3 WEEKS

	HA-Coated	Uncoated
	Interface Shear Strength, MPa	
Control	9.70 (n=2)	3.40 (n=2)
Protein (bOP)	10.75 (n=3)	4.08 (n=3)
	Percent Bone Ingrowth	
Control	42.56 (n=4)	37.82 (n=4)
Protein (bOP)	51.66 (n=4)	46.38 (n=4)

Both the mechanical and histological data suggested that bOP enhanced osseointegration of the implants. Both the HA-coated and uncoated implants showed an increase of shear strength and bone ingrowth compared with untreated controls. Moreover, the HA-coated implants appeared to show significant enhancement compared to the uncoated implant. The histological sections directly showed a greater number of cells between the metal pores.

The positive results of the initial implant study prompted a more detailed study. Twenty-seven implants were treated with a recombinant human OP1 protein. The OP1 protein was produced by transformed CHO cells. Details for the recombinant production of OP1 are disclosed in USSN 841,646, incorporated hereinabove by reference. The protein was purified to contain as the major species the protein designated OP1-18Ser (Seq. ID No. 1, residues 293-431), and about 30% truncated forms of OP1 (e.g., OP1-16Ser, OP1-16Leu, OP1-16Met, OP1-16Ala and OP1-16Val). The protein was greater than 90% pure. The implants were immersed for 30 minutes in

200 µl 50% ethanol/0.01% TFA containing 5 µg recombinant protein and the solution frozen in an ethanol/dry ice bath while the formulation tube was rolled. The tubes were subsequently freeze dried. Nineteen implants were also prepared by treatment with ethanol/TFA without the OP1 protein by the same procedure.

In test implants, it was found that OP1 could be extracted from treated implants with 8M urea, 1% Tween 80, 50mM Tris, pH 8.0 and analyzed by HPLC. By this method, it was shown that all of the OP1 in the formulation tubes bound to the implant under the conditions employed. Furthermore, since the test implants were half coated with HA, additional implants were obtained to independently evaluate the binding of OP1 to each of these surfaces. Initial binding studies showed that the OP1 binds more readily to the HA than to the uncoated metal.

The implants for the second study were evaluated in skeletally mature adult mongrel dogs using the femoral transcortical model. Standard aseptic surgical techniques were used such that each animal received five implants bilaterally. Implantation periods of three weeks were used. The mechanical and quantitative histological data are shown in Table III. Three HA-coated and uncoated configurations were evaluated: controls (no treatment), precoat samples (formulated without OP1) and the OP1 samples.

TABLE III
METAL IMPLANTS - OP-1

	INTERFACE SHEAR ATTACHMENT STRENGTH, MPA		PERCENT BONE INGROWTH	
	3 Weeks:		3 Weeks:	
	HA-coated	Uncoated	HA-coated	Uncoated
Control	7.59±2.99 ($\bar{n}$=10)	6.47±1.23 ($\bar{n}$=10)	44.98±12.57 (n=24)	41.66±11.91 (n=24)
Precoat	7.85±3.43 ($\bar{n}$=9)	6.49±2.20 ($\bar{n}$=9)	40.73±16.88 (n=24)	39.14±16.18 (n=24)
Protein (hOP-1)	8.69±3.17 ($\bar{n}$=17)	6.34±3.04 ($\bar{n}$=17)	48.68±16.61 (n=24)	47.89±11.91 ($\bar{n}$=24)

Mechanical testing results demonstrated enhanced attachment strength for the HA-coated samples as compared to the uncoated samples. At three weeks the greatest fixation was observed with the HA-coated implant with protein.

Histologic analysis demonstrated greater bone ingrowth for all HA-coated versus uncoated samples although the differences were not significant. The percent bone ingrowth was greatest for the HA-coated and uncoated implants with the protein present. Linear regression analysis demonstrated that attachment strength was predicted by amount of bone growth into the porous structure, presence of HA coating, and presence of protein.

Example 2

Titanium frequently is used to fabricate metal prostheses. The surface of these prostheses comprise a layer of titanium oxide. Therefore, titanium oxide itself was evaluated for its ability to serve as a carrier for OP-1 and in general for its biocompatibility with the bone formation process. The *in vivo* biological activity of implants containing a combination of titanium oxide and OP-1 (Sequence ID No. 1, residues 293-431)

was examined in rat subcutaneous and intramuscular assays. Implants contained 0, 6.25, 12.5, 25 or 50 μg of OP-1 formulated onto 30 mg of titanium oxide.

Implants were formulated by a modification of the ethanol/TFA freeze-drying method. Titanium oxide pellets were milled and sieved to a particle size of 250-420 microns. 30 mg of these particles were mixed with 50 μl aliquots of 45% ethanol, 0.09% trifluoroacetic acid containing no OP-1 or various concentrations of OP-1. After 3 hours at 4 °C, the samples were frozen, freeze-dried and implanted into rats.

After 12 days in vivo the implants were removed and evaluated for bone formation by alkaline phosphatase specific activity, calcium content and histological evidence. The results showed that OP-1 induced the formation of bone at each concentration of OP-1 at both the subcutaneous and intramuscular implant sites. No bone formed without OP-1 added to the titanium oxide. The amount of bone as quantitated by calcium content of the implants was similar to that observed using bone collagen carriers. Therefore titanium is a useful carrier for osteogenic proteins and is biocompatible with the bone formation process.

Example 3

The efficacy of the method of this invention on standard dental prosthesis may be assessed using the following model and protocol. Maxillary and mandibular incisor and mandibular canine teeth are extracted from several (e.g., 3) male cynomolgus (Macca fascularis) monkeys (4-6 kilograms) under ketamine anesthesia and local infiltration of lidocaine. Hemostasis is achieved with pressure.

The resultant toothless sockets are filled either with (a) collagen matrix (CM), (b) with collagen matrix containing osteogenic protein, such as the recombinantly produced OP1 protein used in Example 1, above (e.g., an ostegenic device) or c) are left untreated. Titanium, self-tapping, oral,

endosseous implants (Nobelpharma, Chicago, Ill.) are inserted into all of the sockets by minimally engaging the self-tapping tip. The mucoperiosteal flap is released from the underlying tissue and used to obtain primary wound closure using standard surgical procedures known in the medical art.

The animals are sacrificed after three weeks by lethal injection of pentobarbital and perfusion with paraformaldehyde-glutaraldehyde. The jaws then are dissected and the blocks containing the appropriate sockets are resected, further fixed in neutral buffered formalin, decalcified in formic acid and sodium citrate, embedded in plastic and stained with basic Fuchsin and toluidine blue. Sections then are analyzed by light microscopy. Preferably, computer assisted histomorphometric analysis is used to evaluate the new tissue, e.g., using Image 1.27 and Quick Capture^{R} (Data Translation, Inc. Marlboro, MA 07152).

It is anticipated that sockets which contain the osteogenic device will induce the formation of new bone in close apposition to the threaded surface of the titanium implants within 3 weeks. By contrast, sockets treated only with collagen matrix or sockets receiving neither collagen matrix nor the osteogenic device should show no evidence of new bone formation in close apposition to the implant surface.

Equivalents

One skilled in the art will be able to ascertain, using no more than routine experimentation, many equivalents to the subject matter described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Creative BioMolecules, Inc.
(B) STREET: 35 South Street
(C) CITY: Hopkinton
(D) STATE: Massachusetts
(E) COUNTRY: United States
(F) POSTAL CODE (ZIP): 01748
(G) TELEPHONE: 1-508-435-9001
(H) TELEFAX: 1-508-435-0454
(I) TELEX:

(A) NAME: Stryker Biotech
(B) STREET: One Apple Hill
(C) CITY: Natick
(D) STATE: Massachusetts
(E) COUNTRY: United States
(F) POSTAL CODE (ZIP): 01760
(G) TELEPHONE: 1-508-653-2280
(H) TELEFAX: 1-508-653-2770
(I) TELEX:

(ii) TITLE OF INVENTION: PROSTHETIC DEVICES HAVING ENHANCED OSTEOGENIC PROPERTIES

(iii) NUMBER OF SEQUENCES: 22

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Creative BioMolecules, Inc.
(B) STREET: 35 South Street
(C) CITY: Hopkinton
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 01748

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: PITCHER ESQ, EDMUND R
(B) REGISTRATION NUMBER: 27,829
(C) REFERENCE/DOCKET NUMBER: STK-057

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 617/248-7000

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1822 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 49..1341
(C) IDENTIFICATION METHOD: experimental
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "OP1"
/evidence= EXPERIMENTAL
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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  5                  10                  15

CCC CTG TTC CTG CTG CGC TCC GCC CTG GCC GAC TTC AGC CTG GAC AAC      153
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 20                  25                  30                  35

GAG GTG CAC TCG AGC TTC ATC CAC CGG CGC CTC CGC AGC CAG GAG CGG      201
Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg
                 40                  45                  50

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Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg
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Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met
        70                  75                  80

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Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly Gly Pro Gly
  85                  90                  95

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Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly
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ATG GTC ATG AGC TTC GTC AAC CTC GTG GAA CAT GAC AAG GAA TTC TTC      489
Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe
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CAC CCA CGC TAC CAC CAT CGA GAG TTC CGG TTT GAT CTT TCC AAG ATC      537
His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile
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Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp
    165                 170                 175

TAC ATC CGG GAA CGC TTC GAC AAT GAG ACG TTC CGG ATC AGC GTT TAT      633
Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile Ser Val Tyr
180                 185                 190                 195

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Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu Phe Leu Leu
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GAC AGC CGT ACC CTC TGG GCC TCG GAG GAG GGC TGG CTG GTG TTT GAC      729
Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu Val Phe Asp
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        230                 235                 240

GGC CTG CAG CTC TCG GTG GAG ACG CTG GAT GGG CAG AGC ATC AAC CCC      825
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AAG TTG GCG GGC CTG ATT GGG CGG CAC GGG CCC CAG AAC AAG CAG CCC      873
Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys Gln Pro
260                 265                 270                 275

TTC ATG GTG GCT TTC TTC AAG GCC ACG GAG GTC CAC TTC CGC AGC ATC      921
Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe Arg Ser Ile
                280                 285                 290

CGG TCC ACG GGG AGC AAA CAG CGC AGC CAG AAC CGC TCC AAG ACG CCC      969
Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser Lys Thr Pro
            295                 300                 305

AAG AAC CAG GAA GCC CTG CGG ATG GCC AAC GTG GCA GAG AAC AGC AGC     1017
Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu Asn Ser Ser
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AGC GAC CAG AGG CAG GCC TGT AAG AAG CAC GAG CTG TAT GTC AGC TTC      1065
Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe
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Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala
340                 345                 350                 355

GCC TAC TAC TGT GAG GGG GAG TGT GCC TTC CCT CTG AAC TCC TAC ATG      1161
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                360                 365                 370

AAC GCC ACC AAC CAC GCC ATC GTG CAG ACG CTG GTC CAC TTC ATC AAC      1209
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            375                 380                 385

CCG GAA ACG GTG CCC AAG CCC TGC TGT GCG CCC ACG CAG CTC AAT GCC      1257
Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala
        390                 395                 400

ATC TCC GTC CTC TAC TTC GAT GAC AGC TCC AAC GTC ATC CTG AAG AAA      1305
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    405                 410                 415

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Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
420                 425                 430

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TGTGAGAGTA TTAGGAAACA TGAGCAGCAT ATGGCTTTTG ATCAGTTTTT CAGTGGCAGC    1531

ATCCAATGAA CAAGATCCTA CAAGCTGTGC AGGCAAAACC TAGCAGGAAA AAAAAACAAC    1591

GCATAAAGAA AAATGGCCGG GCCAGGTCAT TGGCTGGGAA GTCTCAGCCA TGCACGGACT    1651

CGTTTCCAGA GGTAATTATG AGCGCCTACC AGCCAGGCCA CCCAGCCGTG GGAGGAAGGG    1711

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 431 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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35 40 45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
50 55 60

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
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Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
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Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
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Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
115 120 125

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Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
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Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
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Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
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    370                 375                 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385                 390                 395                 400

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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 96 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..96
(D) OTHER INFORMATION: /note= "COP-5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 96 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..96
(D) OTHER INFORMATION: /note= "COP-7"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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            20                  25                  30

Leu Ala Asp His Leu Asn Ser Thr Asn His Ala Val Val Gln Thr Leu
       35                  40                  45

Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr
    50                  55                  60

Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val
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Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu Gly Cys Gly Cys Arg
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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: DROSOPHILA MELANOGASTER

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..101
(D) OTHER INFORMATION: /label= DPP-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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            20                  25                  30

Lys Cys Pro Phe Pro Leu Ala Asp His Phe Asn Ser Thr Asn His Ala
        35                  40                  45

Val Val Gln Thr Leu Val Asn Asn Asn Asn Pro Gly Lys Val Pro Lys
    50                  55                  60

Ala Cys Cys Val Pro Thr Gln Leu Asp Ser Val Ala Met Leu Tyr Leu
65                  70                  75                  80

Asn Asp Gln Ser Thr Val Val Leu Lys Asn Tyr Gln Glu Met Thr Val
                85                  90                  95

Val Gly Cys Gly Cys Arg
            100
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: XENOPUS

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..102
(D) OTHER INFORMATION: /label= VG1-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Cys Lys Lys Arg His Leu Tyr Val Glu Phe Lys Asp Val Gly Trp Gln
1               5                  10                  15

Asn Trp Val Ile Ala Pro Gln Gly Tyr Met Ala Asn Tyr Cys Tyr Gly
            20                  25                  30

Glu Cys Pro Tyr Pro Leu Thr Glu Ile Leu Asn Gly Ser Asn His Ala
        35                  40                  45

Ile Leu Gln Thr Leu Val His Ser Ile Glu Pro Glu Asp Ile Pro Leu
    50                  55                  60

Pro Cys Cys Val Pro Thr Lys Met Ser Pro Ile Ser Met Leu Phe Tyr
65                  70                  75                  80

Asp Asn Asn Asp Asn Val Val Leu Arg His Tyr Glu Asn Met Ala Val
                85                  90                  95

Asp Glu Cys Gly Cys Arg
            100
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: MURIDAE

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..102
(D) OTHER INFORMATION: /label= VGR-1-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Cys Lys Lys His Gly Leu Tyr Val Ser Phe Gln Asp Val Gly Trp Gln
1               5                  10                  15

Asp Trp Ile Ile Ala Pro Xaa Gly Tyr Ala Ala Asn Tyr Cys Asp Gly
            20                  25                  30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
        35                  40                  45

Ile Val Gln Thr Leu Val His Val Met Asn Pro Glu Tyr Val Pro Lys
    50                  55                  60

Pro Cys Cys Ala Pro Thr Lys Val Asn Ala Ile Ser Val Leu Tyr Phe
65                  70                  75                  80

Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
                85                  90                  95

Arg Ala Cys Gly Cys His
            100
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1873 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: MURIDAE
(F) TISSUE TYPE: EMBRYO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 104..1393
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "MOP1"
/note= "MOP1 (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
CTGCAGCAAG TGACCTCGGG TCGTGGACCG CTGCCCTGCC CCCTCCGCTG CCACCTGGGG      60

CGGCGCGGGC CCGGTGCCCC GGATCGCGCG TAGAGCCGGC GCG ATG CAC GTG CGC      115
                                                Met His Val Arg
                                                  1

TCG CTG CGC GCT GCG GCG CCA CAC AGC TTC GTG GCG CTC TGG GCG CCT      163
Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro
  5                  10                  15                  20

CTG TTC TTG CTG CGC TCC GCC CTG GCC GAT TTC AGC CTG GAC AAC GAG      211
Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn Glu
                  25                  30                  35

GTG CAC TCC AGC TTC ATC CAC CGG CGC CTC CGC AGC CAG GAG CGG CGG      259
Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg Arg
             40                  45                  50

GAG ATG CAG CGG GAG ATC CTG TCC ATC TTA GGG TTG CCC CAT CGC CCG      307
Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg Pro
         55                  60                  65

CGC CCG CAC CTC CAG GGA AAG CAT AAT TCG GCG CCC ATG TTC ATG TTG      355
Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met Leu
     70                  75                  80

GAC CTG TAC AAC GCC ATG GCG GTG GAG GAG AGC GGG CCG GAC GGA CAG      403
Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly Pro Asp Gly Gln
 85                  90                  95                  100

GGC TTC TCC TAC CCC TAC AAG GCC GTC TTC AGT ACC CAG GGC CCC CCT      451
Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly Pro Pro
                 105                 110                 115

TTA GCC AGC CTG CAG GAC AGC CAT TTC CTC ACT GAC GCC GAC ATG GTC      499
Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala Asp Met Val
            120                 125                 130

ATG AGC TTC GTC AAC CTA GTG GAA CAT GAC AAA GAA TTC TTC CAC CCT      547
Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe His Pro
        135                 140                 145

CGA TAC CAC CAT CGG GAG TTC CGG TTT GAT CTT TCC AAG ATC CCC GAG      595
Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile Pro Glu
    150                 155                 160

GGC GAA CGG GTG ACC GCA GCC GAA TTC AGG ATC TAT AAG GAC TAC ATC      643
Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp Tyr Ile
165                 170                 175                 180
```

```
CGG GAG CGA TTT GAC AAC GAG ACC TTC CAG ATC ACA GTC TAT CAG GTG        691
Arg Glu Arg Phe Asp Asn Glu Thr Phe Gln Ile Thr Val Tyr Gln Val
                185                 190                 195

CTC CAG GAG CAC TCA GGC AGG GAG TCG GAC CTC TTC TTG CTG GAC AGC        739
Leu Gln Glu His Ser Gly Arg Glu Ser Asp Leu Phe Leu Leu Asp Ser
            200                 205                 210

CGC ACC ATC TGG GCT TCT GAG GAG GGC TGG TTG GTG TTT GAT ATC ACA        787
Arg Thr Ile Trp Ala Ser Glu Glu Gly Trp Leu Val Phe Asp Ile Thr
        215                 220                 225

GCC ACC AGC AAC CAC TGG GTG GTC AAC CCT CGG CAC AAC CTG GGC TTA        835
Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His Asn Leu Gly Leu
    230                 235                 240

CAG CTC TCT GTG GAG ACC CTG GAT GGG CAG AGC ATC AAC CCC AAG TTG        883
Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile Asn Pro Lys Leu
245                 250                 255                 260

GCA GGC CTG ATT GGA CGG CAT GGA CCC CAG AAC AAG CAA CCC TTC ATG        931
Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys Gln Pro Phe Met
                265                 270                 275

GTG GCC TTC TTC AAG GCC ACG GAA GTC CAT CTC CGT AGT ATC CGG TCC        979
Val Ala Phe Phe Lys Ala Thr Glu Val His Leu Arg Ser Ile Arg Ser
            280                 285                 290

ACG GGG GGC AAG CAG CGC AGC CAG AAT CGC TCC AAG ACG CCA AAG AAC       1027
Thr Gly Gly Lys Gln Arg Ser Gln Asn Arg Ser Lys Thr Pro Lys Asn
        295                 300                 305

CAA GAG GCC CTG AGG ATG GCC AGT GTG GCA GAA AAC AGC AGC AGT GAC       1075
Gln Glu Ala Leu Arg Met Ala Ser Val Ala Glu Asn Ser Ser Ser Asp
    310                 315                 320

CAG AGG CAG GCC TGC AAG AAA CAT GAG CTG TAC GTC AGC TTC CGA GAC       1123
Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp
325                 330                 335                 340

CTT GGC TGG CAG GAC TGG ATC ATT GCA CCT GAA GGC TAT GCT GCC TAC       1171
Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Tyr
                345                 350                 355

TAC TGT GAG GGA GAG TGC GCC TTC CCT CTG AAC TCC TAC ATG AAC GCC       1219
Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met Asn Ala
            360                 365                 370

ACC AAC CAC GCC ATC GTC CAG ACA CTG GTT CAC TTC ATC AAC CCA GAC       1267
Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn Pro Asp
        375                 380                 385
```

```
ACA GTA CCC AAG CCC TGC TGT GCG CCC ACC CAG CTC AAC GCC ATC TCT      1315
Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala Ile Ser
    390                 395                 400

GTC CTC TAC TTC GAC GAC AGC TCT AAT GTC GAC CTG AAG AAG TAC AGA      1363
Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Asp Leu Lys Lys Tyr Arg
405                 410                 415                 420

AAC ATG GTG GTC CGG GCC TGT GGC TGC CAC TAGCTCTTCC TGAGACCCTG        1413
Asn Met Val Val Arg Ala Cys Gly Cys His
                425                 430

ACCTTTGCGG GGCCACACCT TTCCAAATCT TCGATGTCTC ACCATCTAAG TCTCTCACTG    1473

CCCACCTTGG CGAGGAGAAC AGACCAACCT CTCCTGAGCC TTCCCTCACC TCCCAACCGG    1533

AAGCATGTAA GGGTTCCAGA AACCTGAGCG TGCAGCAGCT GATGAGCGCC CTTTCCTTCT    1593

GGCACGTGAC GGACAAGATC CTACCAGCTA CCACAGCAAA CGCCTAAGAG CAGGAAAAAT    1653

GTCTGCCAGG AAAGTGTCCA GTGTCCACAT GGCCCCTGGC GCTCTGAGTC TTTGAGGAGT    1713

AATCGCAAGC CTCGTTCAGC TGCAGCAGAA GGAAGGGCTT AGCCAGGGTG GGCGCTGGCG    1773

TCTGTGTTGA AGGGAAACCA AGCAGAAGCC ACTGTAATGA TATGTCACAA TAAAACCCAT    1833

GAATGAAAAA AAAAAAAAAA AAAAAAAAAA AAAAGAATTC                          1873
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 430 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala
 1               5                  10                  15

Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser
            20                  25                  30

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
        35                  40                  45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
    50                  55                  60
```

```
Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
 65                  70                  75                  80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly
                85                  90                  95

Pro Asp Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr
            100                 105                 110

Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp
        115                 120                 125

Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu
    130                 135                 140

Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser
145                 150                 155                 160

Lys Ile Pro Glu Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr
                165                 170                 175

Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Gln Ile Thr
            180                 185                 190

Val Tyr Gln Val Leu Gln Glu His Ser Gly Arg Glu Ser Asp Leu Phe
        195                 200                 205

Leu Leu Asp Ser Arg Thr Ile Trp Ala Ser Glu Glu Gly Trp Leu Val
    210                 215                 220

Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His
225                 230                 235                 240

Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile
                245                 250                 255

Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys
            260                 265                 270

Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Leu Arg
        275                 280                 285

Ser Ile Arg Ser Thr Gly Gly Lys Gln Arg Ser Gln Asn Arg Ser Lys
    290                 295                 300

Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Ser Val Ala Glu Asn
305                 310                 315                 320

Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val
                325                 330                 335

Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly
            340                 345                 350
```

```
Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser
      355                 360                 365

Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe
    370                 375                 380

Ile Asn Pro Asp Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu
385                 390                 395                 400

Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Asp Leu
                405                 410                 415

Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
            420                 425                 430
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1723 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 490..1696
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "hOP2-PP"
/note= "hOP2 (cDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
GGCGCCGGCA GAGCAGGAGT GGCTGGAGGA GCTGTGGTTG GAGCAGGAGG TGGCACGGCA      60

GGGCTGGAGG GCTCCCTATG AGTGGCGGAG ACGGCCCAGG AGGCGCTGGA GCAACAGCTC     120

CCACACCGCA CCAAGCGGTG GCTGCAGGAG CTCGCCCATC GCCCCTGCGC TGCTCGGACC     180

GCGGCCACAG CCGGACTGGC GGGTACGGCG GCGACAGAGG CATTGGCCGA GAGTCCCAGT     240

CCGCAGAGTA GCCCCGGCCT CGAGGCGGTG GCGTCCCGGT CCTCTCCGTC CAGGAGCCAG     300

GACAGGTGTC GCGCGGCGGG GCTCCAGGGA CCGCGCCTGA GGCCGGCTGC CCGCCCGTCC     360

CGCCCCGCCC CGCCGCCCGC CGCCCGCCGA GCCCAGCCTC CTTGCCGTCG GGGCGTCCCC     420
```

```
AGGCCCTGGG TCGGCCGCGG AGCCGATGCG CGCCCGCTGA GCGCCCCAGC TGAGCGCCCC      480

CGGCCTGCC ATG ACC GCG CTC CCC GGC CCG CTC TGG CTC CTG GGC CTG          528
          Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu
            1               5                  10

GCG CTA TGC GCG CTG GGC GGG GGC GGC CCC GGC CTG CGA CCC CCG CCC        576
Ala Leu Cys Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro
     15                  20                  25

GGC TGT CCC CAG CGA CGT CTG GGC GCG CGC GAG CGC CGG GAC GTG CAG        624
Gly Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln
 30                  35                  40                  45

CGC GAG ATC CTG GCG GTG CTC GGG CTG CCT GGG CGG CCC CGG CCC CGC        672
Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg
                50                  55                  60

GCG CCA CCC GCC GCC TCC CGG CTG CCC GCG TCC GCG CCG CTC TTC ATG        720
Ala Pro Pro Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met
            65                  70                  75

CTG GAC CTG TAC CAC GCC ATG GCC GGC GAC GAC GAC GAG GAC GGC GCG        768
Leu Asp Leu Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala
        80                  85                  90

CCC GCG GAG CGG CGC CTG GGC CGC GCC GAC CTG GTC ATG AGC TTC GTT        816
Pro Ala Glu Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val
     95                  100                 105

AAC ATG GTG GAG CGA GAC CGT GCC CTG GGC CAC CAG GAG CCC CAT TGG        864
Asn Met Val Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp
110                 115                 120                 125

AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT GGG GAG GCG GTC        912
Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val
                130                 135                 140

ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC CTG CTC        960
Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu
            145                 150                 155

AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC       1008
Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser
        160                 165                 170

AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT       1056
Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala
    175                 180                 185
```

```
GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC ACA GCA GCC AGT GAC TGC      1104
Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys
190                 195                 200                 205

TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA CTC CGC CTC TAT GTG GAG      1152
Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu
                210                 215                 220

ACT GAG GAC GGG CAC AGC GTG GAT CCT GGC CTG GCC GGC CTG CTG GGT      1200
Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly
            225                 230                 235

CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC GTG GTC ACT TTC TTC AGG      1248
Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg
        240                 245                 250

GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG GCA GTG AGG CCA CTG AGG      1296
Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg
    255                 260                 265

AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG CCG CAG GCC AAC CGA CTC      1344
Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu
270                 275                 280                 285

CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC CAC GGC CGG CAG GTC TGC      1392
Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys
                290                 295                 300

CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG GAC CTC GGC TGG CTG GAC      1440
Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp
            305                 310                 315

TGG GTC ATC GCT CCC CAA GGC TAC TCG GCC TAT TAC TGT GAG GGG GAG      1488
Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu
        320                 325                 330

TGC TCC TTC CCA CTG GAC TCC TGC ATG AAT GCC ACC AAC CAC GCC ATC      1536
Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile
    335                 340                 345

CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA AAC GCA GTC CCC AAG GCG      1584
Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala
350                 355                 360                 365

TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC TCT GTG CTC TAC TAT GAC      1632
Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp
                370                 375                 380

AGC AGC AAC AAC GTC ATC CTG CGC AAA GCC CGC AAC ATG GTG GTC AAG      1680
Ser Ser Asn Asn Val Ile Leu Arg Lys Ala Arg Asn Met Val Val Lys
            385                 390                 395
```

GCC TGC GGC TGC CAC T GAGTCAGCCC GCCCAGCCCT ACTGCAG 1723
Ala Cys Gly Cys His
400

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 402 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys
1 5 10 15

Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro Gly Cys Pro
20 25 30

Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln Arg Glu Ile
35 40 45

Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Pro Pro
50 55 60

Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu
65 70 75 80

Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala Pro Ala Glu
85 90 95

Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val
100 105 110

Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp Lys Glu Phe
115 120 125

Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala
130 135 140

Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu Asn Arg Thr
145 150 155 160

Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser Asn Arg Glu
165 170 175

Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp Glu
180 185 190

```
Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys Trp Leu Leu
        195                 200                 205

Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Glu Asp
    210                 215                 220

Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala
225                 230                 235                 240

Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg Ala Ser Pro
                245                 250                 255

Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg Arg Arg Gln
            260                 265                 270

Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu Pro Gly Ile
        275                 280                 285

Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His
    290                 295                 300

Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp Val Ile
305                 310                 315                 320

Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe
                325                 330                 335

Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser
            340                 345                 350

Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala Cys Cys Ala
        355                 360                 365

Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn
    370                 375                 380

Asn Val Ile Leu Arg Lys Ala Arg Asn Met Val Val Lys Ala Cys Gly
385                 390                 395                 400

Cys His
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1926 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:
(A) ORGANISM: MURIDAE
(F) TISSUE TYPE: EMBRYO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 93..1289
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "mOP2-PP"
/note= "mOP2 cDNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
GCCAGGCACA GGTGCGCCGT CTGGTCCTCC CCGTCTGGCG TCAGCCGAGC CCGACCAGCT      60

ACCAGTGGAT GCGCGCCGGC TGAAAGTCCG AG ATG GCT ATG CGT CCC GGG CCA      113
                                    Met Ala Met Arg Pro Gly Pro
                                      1               5

CTC TGG CTA TTG GGC CTT GCT CTG TGC GCG CTG GGA GGC GGC CAC GGT      161
Leu Trp Leu Leu Gly Leu Ala Leu Cys Ala Leu Gly Gly Gly His Gly
         10                  15                  20

CCG CGT CCC CCG CAC ACC TGT CCC CAG CGT CGC CTG GGA GCG CGC GAG      209
Pro Arg Pro Pro His Thr Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu
     25                  30                  35

CGC CGC GAC ATG CAG CGT GAA ATC CTG GCG GTG CTC GGG CTA CCG GGA      257
Arg Arg Asp Met Gln Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly
 40                  45                  50                  55

CGG CCC CGA CCC CGT GCA CAA CCC GCC GCT GCC CGG CAG CCA GCG TCC      305
Arg Pro Arg Pro Arg Ala Gln Pro Ala Ala Ala Arg Gln Pro Ala Ser
                 60                  65                  70

GCG CCC CTC TTC ATG TTG GAC CTA TAC CAC GCC ATG ACC GAT GAC GAC      353
Ala Pro Leu Phe Met Leu Asp Leu Tyr His Ala Met Thr Asp Asp Asp
             75                  80                  85

GAC GGC GGG CCA CCA CAG GCT CAC TTA GGC CGT GCC GAC CTG GTC ATG      401
Asp Gly Gly Pro Pro Gln Ala His Leu Gly Arg Ala Asp Leu Val Met
         90                  95                  100

AGC TTC GTC AAC ATG GTG GAA CGC GAC CGT ACC CTG GGC TAC CAG GAG      449
Ser Phe Val Asn Met Val Glu Arg Asp Arg Thr Leu Gly Tyr Gln Glu
     105                 110                 115

CCA CAC TGG AAG GAA TTC CAC TTT GAC CTA ACC CAG ATC CCT GCT GGG      497
Pro His Trp Lys Glu Phe His Phe Asp Leu Thr Gln Ile Pro Ala Gly
120                 125                 130                 135

GAG GCT GTC ACA GCT GCT GAG TTC CGG ATC TAC AAA GAA CCC AGC ACC      545
Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Glu Pro Ser Thr
                140                 145                 150
```

```
CAC CCG CTC AAC ACA ACC CTC CAC ATC AGC ATG TTC GAA GTG GTC CAA      593
His Pro Leu Asn Thr Thr Leu His Ile Ser Met Phe Glu Val Val Gln
            155                 160                 165

GAG CAC TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG      641
Glu His Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr
        170                 175                 180

CTC CGA TCT GGG GAC GAG GGC TGG CTG GTG CTG GAC ATC ACA GCA GCC      689
Leu Arg Ser Gly Asp Glu Gly Trp Leu Val Leu Asp Ile Thr Ala Ala
    185                 190                 195

AGT GAC CGA TGG CTG CTG AAC CAT CAC AAG GAC CTG GGA CTC CGC CTC      737
Ser Asp Arg Trp Leu Leu Asn His His Lys Asp Leu Gly Leu Arg Leu
200                 205                 210                 215

TAT GTG GAA ACC GCG GAT GGG CAC AGC ATG GAT CCT GGC CTG GCT GGT      785
Tyr Val Glu Thr Ala Asp Gly His Ser Met Asp Pro Gly Leu Ala Gly
                220                 225                 230

CTG CTT GGA CGA CAA GCA CCA CGC TCC AGA CAG CCT TTC ATG GTA ACC      833
Leu Leu Gly Arg Gln Ala Pro Arg Ser Arg Gln Pro Phe Met Val Thr
            235                 240                 245

TTC TTC AGG GCC AGC CAG AGT CCT GTG CGG GCC CCT CGG GCA GCG AGA      881
Phe Phe Arg Ala Ser Gln Ser Pro Val Arg Ala Pro Arg Ala Ala Arg
        250                 255                 260

CCA CTG AAG AGG AGG CAG CCA AAG AAA ACG AAC GAG CTT CCG CAC CCC      929
Pro Leu Lys Arg Arg Gln Pro Lys Lys Thr Asn Glu Leu Pro His Pro
    265                 270                 275

AAC AAA CTC CCA GGG ATC TTT GAT GAT GGC CAC GGT TCC CGC GGC AGA      977
Asn Lys Leu Pro Gly Ile Phe Asp Asp Gly His Gly Ser Arg Gly Arg
280                 285                 290                 295

GAG GTT TGC CGC AGG CAT GAG CTC TAC GTC AGC TTC CGT GAC CTT GGC     1025
Glu Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly
                300                 305                 310

TGG CTG GAC TGG GTC ATC GCC CCC CAG GGC TAC TCT GCC TAT TAC TGT     1073
Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys
            315                 320                 325

GAG GGG GAG TGT GCT TTC CCA CTG GAC TCC TGT ATG AAC GCC ACC AAC     1121
Glu Gly Glu Cys Ala Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn
        330                 335                 340

CAT GCC ATC TTG CAG TCT CTG GTG CAC CTG ATG AAG CCA GAT GTT GTC     1169
His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asp Val Val
    345                 350                 355
```

```
CCC AAG GCA TGC TGT GCA CCC ACC AAA CTG AGT GCC ACC TCT GTG CTG      1217
Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val Leu
360                 365                 370                 375

TAC TAT GAC AGC AGC AAC AAT GTC ATC CTG CGT AAA CAC CGT AAC ATG      1265
Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn Met
                380                 385                 390

GTG GTC AAG GCC TGT GGC TGC CAC TGAGGCCCCG CCCAGCATCC TGCTTCTACT     1319
Val Val Lys Ala Cys Gly Cys His
            395

ACCTTACCAT CTGGCCGGGC CCCTCTCCAG AGGCAGAAAC CCTTCTATGT TATCATAGCT    1379

CAGACAGGGG CAATGGGAGG CCCTTCACTT CCCCTGGCCA CTTCCTGCTA AAATTCTGGT    1439

CTTTCCCAGT TCCTCTGTCC TTCATGGGGT TTCGGGGCTA TCACCCCGCC CTCTCCATCC    1499

TCCTACCCCA AGCATAGACT GAATGCACAC AGCATCCCAG AGCTATGCTA ACTGAGAGGT    1559

CTGGGGTCAG CACTGAAGGC CCACATGAGG AAGACTGATC CTTGGCCATC CTCAGCCCAC    1619

AATGGCAAAT TCTGGATGGT CTAAGAAGGC CCTGGAATTC TAAACTAGAT GATCTGGGCT    1679

CTCTGCACCA TTCATTGTGG CAGTTGGGAC ATTTTTAGGT ATAACAGACA CATACACTTA    1739

GATCAATGCA TCGCTGTACT CCTTGAAATC AGAGCTAGCT TGTTAGAAAA AGAATCAGAG    1799

CCAGGTATAG CGGTGCATGT CATTAATCCC AGCGCTAAAG AGACAGAGAC AGGAGAATCT    1859

CTGTGAGTTC AAGGCCACAT AGAAAGAGCC TGTCTCGGGA GCAGGAAAAA AAAAAAAAAC    1919

GGAATTC                                                              1926
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 399 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Met Ala Met Arg Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys
 1               5                  10                  15

Ala Leu Gly Gly Gly His Gly Pro Arg Pro Pro His Thr Cys Pro Gln
            20                  25                  30
```

```
Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Met Gln Arg Glu Ile Leu
        35                  40                  45

Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Gln Pro Ala
    50                  55                  60

Ala Ala Arg Gln Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr
65                  70                  75                  80

His Ala Met Thr Asp Asp Asp Asp Gly Gly Pro Pro Gln Ala His Leu
                85                  90                  95

Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val Glu Arg Asp
            100                 105                 110

Arg Thr Leu Gly Tyr Gln Glu Pro His Trp Lys Glu Phe His Phe Asp
        115                 120                 125

Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg
    130                 135                 140

Ile Tyr Lys Glu Pro Ser Thr His Pro Leu Asn Thr Thr Leu His Ile
145                 150                 155                 160

Ser Met Phe Glu Val Val Gln Glu His Ser Asn Arg Glu Ser Asp Leu
                165                 170                 175

Phe Phe Leu Asp Leu Gln Thr Leu Arg Ser Gly Asp Glu Gly Trp Leu
            180                 185                 190

Val Leu Asp Ile Thr Ala Ala Ser Asp Arg Trp Leu Leu Asn His His
        195                 200                 205

Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Ala Asp Gly His Ser
    210                 215                 220

Met Asp Pro Gly Leu Ala Gly Leu Leu Gly Arg Gln Ala Pro Arg Ser
225                 230                 235                 240

Arg Gln Pro Phe Met Val Thr Phe Phe Arg Ala Ser Gln Ser Pro Val
                245                 250                 255

Arg Ala Pro Arg Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys
            260                 265                 270

Thr Asn Glu Leu Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp
        275                 280                 285

Gly His Gly Ser Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr
    290                 295                 300

Val Ser Phe Arg Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln
305                 310                 315                 320
```

```
Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp
                325                 330                 335

Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His
            340                 345                 350

Leu Met Lys Pro Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys
        355                 360                 365

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile
    370                 375                 380

Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1260 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 9..1196
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "BMP2A"
/note= "BMP2A (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
GGTCGACC ATG GTG GCC GGG ACC CGC TGT CTT CTA GCG TTG CTG CTT CCC       50
         Met Val Ala Gly Thr Arg Cys Leu Leu Ala Leu Leu Leu Pro
           1               5                  10

CAG GTC CTC CTG GGC GGC GCG GCT GGC CTC GTT CCG GAG CTG GGC CGC       98
Gln Val Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg
 15                  20                  25                  30
```

```
AGG AAG TTC GCG GCG GCG TCG TCG GGC CGC CCC TCA TCC CAG CCC TCT      146
Arg Lys Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser
                35                  40                  45

GAC GAG GTC CTG AGC GAG TTC GAG TTG CGG CTG CTC AGC ATG TTC GGC      194
Asp Glu Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly
            50                  55                  60

CTG AAA CAG AGA CCC ACC CCC AGC AGG GAC GCC GTG GTG CCC CCC TAC      242
Leu Lys Gln Arg Pro Thr Pro Ser Arg Asp Ala Val Val Pro Pro Tyr
        65                  70                  75

ATG CTA GAC CTG TAT CGC AGG CAC TCG GGT CAG CCG GGC TCA CCC GCC      290
Met Leu Asp Leu Tyr Arg Arg His Ser Gly Gln Pro Gly Ser Pro Ala
    80                  85                  90

CCA GAC CAC CGG TTG GAG AGG GCA GCC AGC CGA GCC AAC ACT GTG CGC      338
Pro Asp His Arg Leu Glu Arg Ala Ala Ser Arg Ala Asn Thr Val Arg
95                  100                 105                 110

AGC TTC CAC CAT GAA GAA TCT TTG GAA GAA CTA CCA GAA ACG AGT GGG      386
Ser Phe His His Glu Glu Ser Leu Glu Glu Leu Pro Glu Thr Ser Gly
                115                 120                 125

AAA ACA ACC CGG AGA TTC TTC TTT AAT TTA AGT TCT ATC CCC ACG GAG      434
Lys Thr Thr Arg Arg Phe Phe Phe Asn Leu Ser Ser Ile Pro Thr Glu
            130                 135                 140

GAG TTT ATC ACC TCA GCA GAG CTT CAG GTT TTC CGA GAA CAG ATG CAA      482
Glu Phe Ile Thr Ser Ala Glu Leu Gln Val Phe Arg Glu Gln Met Gln
        145                 150                 155

GAT GCT TTA GGA AAC AAT AGC AGT TTC CAT CAC CGA ATT AAT ATT TAT      530
Asp Ala Leu Gly Asn Asn Ser Ser Phe His His Arg Ile Asn Ile Tyr
    160                 165                 170

GAA ATC ATA AAA CCT GCA ACA GCC AAC TCG AAA TTC CCC GTG ACC AGT      578
Glu Ile Ile Lys Pro Ala Thr Ala Asn Ser Lys Phe Pro Val Thr Ser
175                 180                 185                 190

CTT TTG GAC ACC AGG TTG GTG AAT CAG AAT GCA AGC AGG TGG GAA AGT      626
Leu Leu Asp Thr Arg Leu Val Asn Gln Asn Ala Ser Arg Trp Glu Ser
                195                 200                 205

TTT GAT GTC ACC CCC GCT GTG ATG CGG TGG ACT GCA CAG GGA CAC GCC      674
Phe Asp Val Thr Pro Ala Val Met Arg Trp Thr Ala Gln Gly His Ala
            210                 215                 220

AAC CAT GGA TTC GTG GTG GAA GTG GCC CAC TTG GAG GAG AAA CAA GGT      722
Asn His Gly Phe Val Val Glu Val Ala His Leu Glu Glu Lys Gln Gly
        225                 230                 235
```

```
GTC TCC AAG AGA CAT GTT AGG ATA AGC AGG TCT TTG CAC CAA GAT GAA      770
Val Ser Lys Arg His Val Arg Ile Ser Arg Ser Leu His Gln Asp Glu
    240                 245                 250

CAC AGC TGG TCA CAG ATA AGG CCA TTG CTA GTA ACT TTT GGC CAT GAT      818
His Ser Trp Ser Gln Ile Arg Pro Leu Leu Val Thr Phe Gly His Asp
255                 260                 265                 270

GGA AAA GGG CAT CCT CTC CAC AAA AGA GAA AAA CGT CAA GCC AAA CAC      866
Gly Lys Gly His Pro Leu His Lys Arg Glu Lys Arg Gln Ala Lys His
                275                 280                 285

AAA CAG CGG AAA CGC CTT AAG TCC AGC TGT AAG AGA CAC CCT TTG TAC      914
Lys Gln Arg Lys Arg Leu Lys Ser Ser Cys Lys Arg His Pro Leu Tyr
            290                 295                 300

GTG GAC TTC AGT GAC GTG GGG TGG AAT GAC TGG ATT GTG GCT CCC CCG      962
Val Asp Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro
        305                 310                 315

GGG TAT CAC GCC TTT TAC TGC CAC GGA GAA TGC CCT TTT CCT CTG GCT     1010
Gly Tyr His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala
    320                 325                 330

GAT CAT CTG AAC TCC ACT AAT CAT GCC ATT GTT CAG ACG TTG GTC AAC     1058
Asp His Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn
335                 340                 345                 350

TCT GTT AAC TCT AAG ATT CCT AAG GCA TGC TGT GTC CCG ACA GAA CTC     1106
Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu
                355                 360                 365

AGT GCT ATC TCG ATG CTG TAC CTT GAC GAG AAT GAA AAG GTT GTA TTA     1154
Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu
            370                 375                 380

AAG AAC TAT CAG GAT ATG GTT GTG GAG GGT TGT GGG TGT CGC             1196
Lys Asn Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg
        385                 390                 395

TAGTACAGCA AAATTAAATA CATAAATATA TATATATATA TATATTTTAG AAAAAAGAAA    1256

AAAA                                                                1260
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 396 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Met Val Ala Gly Thr Arg Cys Leu Leu Ala Leu Leu Leu Pro Gln Val
 1               5                  10                  15

Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg Arg Lys
            20                  25                  30

Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser Asp Glu
        35                  40                  45

Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly Leu Lys
    50                  55                  60

Gln Arg Pro Thr Pro Ser Arg Asp Ala Val Val Pro Pro Tyr Met Leu
65                  70                  75                  80

Asp Leu Tyr Arg Arg His Ser Gly Gln Pro Gly Ser Pro Ala Pro Asp
                85                  90                  95

His Arg Leu Glu Arg Ala Ala Ser Arg Ala Asn Thr Val Arg Ser Phe
            100                 105                 110

His His Glu Glu Ser Leu Glu Glu Leu Pro Glu Thr Ser Gly Lys Thr
        115                 120                 125

Thr Arg Arg Phe Phe Phe Asn Leu Ser Ser Ile Pro Thr Glu Glu Phe
    130                 135                 140

Ile Thr Ser Ala Glu Leu Gln Val Phe Arg Glu Gln Met Gln Asp Ala
145                 150                 155                 160

Leu Gly Asn Asn Ser Ser Phe His His Arg Ile Asn Ile Tyr Glu Ile
                165                 170                 175

Ile Lys Pro Ala Thr Ala Asn Ser Lys Phe Pro Val Thr Ser Leu Leu
            180                 185                 190

Asp Thr Arg Leu Val Asn Gln Asn Ala Ser Arg Trp Glu Ser Phe Asp
        195                 200                 205

Val Thr Pro Ala Val Met Arg Trp Thr Ala Gln Gly His Ala Asn His
    210                 215                 220

Gly Phe Val Val Glu Val Ala His Leu Glu Glu Lys Gln Gly Val Ser
225                 230                 235                 240

Lys Arg His Val Arg Ile Ser Arg Ser Leu His Gln Asp Glu His Ser
                245                 250                 255
```

```
Trp Ser Gln Ile Arg Pro Leu Leu Val Thr Phe Gly His Asp Gly Lys
            260                 265                 270

Gly His Pro Leu His Lys Arg Glu Lys Arg Gln Ala Lys His Lys Gln
        275                 280                 285

Arg Lys Arg Leu Lys Ser Ser Cys Lys Arg His Pro Leu Tyr Val Asp
    290                 295                 300

Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr
305                 310                 315                 320

His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala Asp His
                325                 330                 335

Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val
            340                 345                 350

Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala
        355                 360                 365

Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu Lys Asn
    370                 375                 380

Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 574 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..327
(D) OTHER INFORMATION: /product= "MATURE hBMP3 (PARTIAL)"
/note= "THIS PARTIAL SEQUENCE OF THE MATURE HUMAN BMP3 PROTEIN INCLUDES THE FIRST THREE CYSTEINES OF THE CONSERVED 7 CYSTEINE SKELETON. SEE U.S. PAT. NO. 5,011,691 FOR 102 C-TERMINAL SEQUENCE (CBMP3.)"

(ix) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 328..574

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
CGA GCT TCT AAA ATA GAA TAC CAG TAT AAA AAG GAT GAG GTG TGG GAG      48
Arg Ala Ser Lys Ile Glu Tyr Gln Tyr Lys Lys Asp Glu Val Trp Glu
 1               5                  10                  15

GAG AGA AAG CCT TAC AAG ACC CTT CAG GGC TCA GGC CCT GAA AAG AGT      96
Glu Arg Lys Pro Tyr Lys Thr Leu Gln Gly Ser Gly Pro Glu Lys Ser
            20                  25                  30

AAG AAT AAA AAG AAA CAG AGA AAG GGG CCT CAT CGG AAG AGC CAG ACG     144
Lys Asn Lys Lys Lys Gln Arg Lys Gly Pro His Arg Lys Ser Gln Thr
        35                  40                  45

CTC CAA TTT GAT GAG CAG ACC CTG AAA AAG GCA AGG AGA AAG CAG TGG     192
Leu Gln Phe Asp Glu Gln Thr Leu Lys Lys Ala Arg Arg Lys Gln Trp
    50                  55                  60

ATT GAA CCT CGG AAT TGC GCC AGG AGA TAC CTC AAG GTA GAC TTT GCA     240
Ile Glu Pro Arg Asn Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala
65                  70                  75                  80

GAT ATT GGC TGG AGT GAA TGG ATT ATC TCC CCC AAG TCC TTT GAT GCC     288
Asp Ile Gly Trp Ser Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala
                85                  90                  95

TAT TAT TGC TCT GGA GCA TGC CAG TTC CCC ATG CCA AAG GTAGCCATTG     337
Tyr Tyr Cys Ser Gly Ala Cys Gln Phe Pro Met Pro Lys
            100                 105

TTCTCTGTCC TGTACTTACT TCCTATTTCC ATTAGTAGAA AGACACATTG ACTAAGTTAG   397

TGTGCATATA GGGGGTTTGT GTAAGTGTTT GTGTTTCCAT TTGCAAAATC CATTGGGACC   457

CTTATTTACT ACATTCTAAA CCATAATAGG TAATATGGTT ATTCTTGGTT TCTCTTTAAT   517

GGTTGTTAAA GTCATATGAA GTCAGTATTG GTATAAAGAA GGATATGAGA AAAAAAA      574
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
Arg Ala Ser Lys Ile Glu Tyr Gln Tyr Lys Lys Asp Glu Val Trp Glu
 1               5                  10                  15
```

```
Glu Arg Lys Pro Tyr Lys Thr Leu Gln Gly Ser Gly Pro Glu Lys Ser
            20                  25                  30

Lys Asn Lys Lys Lys Gln Arg Lys Gly Pro His Arg Lys Ser Gln Thr
        35                  40                  45

Leu Gln Phe Asp Glu Gln Thr Leu Lys Lys Ala Arg Arg Lys Gln Trp
    50                  55                  60

Ile Glu Pro Arg Asn Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala
65                  70                  75                  80

Asp Ile Gly Trp Ser Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala
                85                  90                  95

Tyr Tyr Cys Ser Gly Ala Cys Gln Phe Pro Met Pro Lys
            100                 105
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1788 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 403..1626
(C) IDENTIFICATION METHOD: experimental
(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"
/product= "BMP2B"
/evidence= EXPERIMENTAL
/note= "BMP2B (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
GAATTCGGGG CAGAGGAGGA GGGAGGGAGG GAAGGAGCGC GGAGCCCGGC CCGGAAGCTA      60

GGTGAGTGTG GCATCCGAGC TGAGGGACGC GAGCCTGAGA CGCCGCTGCT GCTCCGGCTG     120

AGTATCTAGC TTGTCTCCCC GATGGGATTC CCGTCCAAGC TATCTCGAGC CTGCAGCGCC     180
```

```
ACAGTCCCCG GCCCTCGCCC AGGTTCACTG CAACCGTTCA GAGGTCCCCA GGAGCTGCTG      240

CTGGCGAGCC CGCTACTGCA GGGACCTATG GAGCCATTCC GTAGTGCCAT CCCGAGCAAC      300

GCACTGCTGC AGCTTCCCTG AGCCTTTCCA GCAAGTTTGT TCAAGATTGG CTGTCAAGAA      360

TCATGGACTG TTATTATATG CCTTGTTTTC TGTCAAGACA CC ATG ATT CCT GGT          414
                                               Met Ile Pro Gly
                                                 1

AAC CGA ATG CTG ATG GTC GTT TTA TTA TGC CAA GTC CTG CTA GGA GGC         462
Asn Arg Met Leu Met Val Val Leu Leu Cys Gln Val Leu Leu Gly Gly
  5                  10                  15                  20

GCG AGC CAT GCT AGT TTG ATA CCT GAG ACG GGG AAG AAA AAA GTC GCC         510
Ala Ser His Ala Ser Leu Ile Pro Glu Thr Gly Lys Lys Lys Val Ala
                  25                  30                  35

GAG ATT CAG GGC CAC GCG GGA GGA CGC CGC TCA GGG CAG AGC CAT GAG         558
Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly Gln Ser His Glu
             40                  45                  50

CTC CTG CGG GAC TTC GAG GCG ACA CTT CTG CAG ATG TTT GGG CTG CGC         606
Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met Phe Gly Leu Arg
         55                  60                  65

CGC CGC CCG CAG CCT AGC AAG AGT GCC GTC ATT CCG GAC TAC ATG CGG         654
Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro Asp Tyr Met Arg
     70                  75                  80

GAT CTT TAC CGG CTT CAG TCT GGG GAG GAG GAG GAA GAG CAG ATC CAC         702
Asp Leu Tyr Arg Leu Gln Ser Gly Glu Glu Glu Glu Glu Gln Ile His
 85                  90                  95                  100

AGC ACT GGT CTT GAG TAT CCT GAG CGC CCG GCC AGC CGG GCC AAC ACC         750
Ser Thr Gly Leu Glu Tyr Pro Glu Arg Pro Ala Ser Arg Ala Asn Thr
                 105                 110                 115

GTG AGG AGC TTC CAC CAC GAA GAA CAT CTG GAG AAC ATC CCA GGG ACC         798
Val Arg Ser Phe His His Glu Glu His Leu Glu Asn Ile Pro Gly Thr
             120                 125                 130

AGT GAA AAC TCT GCT TTT CGT TTC CTC TTT AAC CTC AGC AGC ATC CCT         846
Ser Glu Asn Ser Ala Phe Arg Phe Leu Phe Asn Leu Ser Ser Ile Pro
         135                 140                 145

GAG AAC GAG GTG ATC TCC TCT GCA GAG CTT CGG CTC TTC CGG GAG CAG         894
Glu Asn Glu Val Ile Ser Ser Ala Glu Leu Arg Leu Phe Arg Glu Gln
     150                 155                 160
```

```
GTG GAC CAG GGC CCT GAT TGG GAA AGG GGC TTC CAC CGT ATA AAC ATT      942
Val Asp Gln Gly Pro Asp Trp Glu Arg Gly Phe His Arg Ile Asn Ile
165                 170                 175                 180

TAT GAG GTT ATG AAG CCC CCA GCA GAA GTG GTG CCT GGG CAC CTC ATC      990
Tyr Glu Val Met Lys Pro Pro Ala Glu Val Val Pro Gly His Leu Ile
                185                 190                 195

ACA CGA CTA CTG GAC ACG AGA CTG GTC CAC CAC AAT GTG ACA CGG TGG     1038
Thr Arg Leu Leu Asp Thr Arg Leu Val His His Asn Val Thr Arg Trp
            200                 205                 210

GAA ACT TTT GAT GTG AGC CCT GCG GTC CTT CGC TGG ACC CGG GAG AAG     1086
Glu Thr Phe Asp Val Ser Pro Ala Val Leu Arg Trp Thr Arg Glu Lys
        215                 220                 225

CAG CCA AAC TAT GGG CTA GCC ATT GAG GTG ACT CAC CTC CAT CAG ACT     1134
Gln Pro Asn Tyr Gly Leu Ala Ile Glu Val Thr His Leu His Gln Thr
    230                 235                 240

CGG ACC CAC CAG GGC CAG CAT GTC AGG ATT AGC CGA TCG TTA CCT CAA     1182
Arg Thr His Gln Gly Gln His Val Arg Ile Ser Arg Ser Leu Pro Gln
245                 250                 255                 260

GGG AGT GGG AAT TGG GCC CAG CTC CGG CCC CTC CTG GTC ACC TTT GGC     1230
Gly Ser Gly Asn Trp Ala Gln Leu Arg Pro Leu Leu Val Thr Phe Gly
                265                 270                 275

CAT GAT GGC CGG GGC CAT GCC TTG ACC CGA CGC CGG AGG GCC AAG CGT     1278
His Asp Gly Arg Gly His Ala Leu Thr Arg Arg Arg Arg Ala Lys Arg
            280                 285                 290

AGC CCT AAG CAT CAC TCA CAG CGG GCC AGG AAG AAG AAT AAG AAC TGC     1326
Ser Pro Lys His His Ser Gln Arg Ala Arg Lys Lys Asn Lys Asn Cys
        295                 300                 305

CGG CGC CAC TCG CTC TAT GTG GAC TTC AGC GAT GTG GGC TGG AAT GAC     1374
Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn Asp
    310                 315                 320

TGG ATT GTG GCC CCA CCA GGC TAC CAG GCC TTC TAC TGC CAT GGG GAC     1422
Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr Cys His Gly Asp
325                 330                 335                 340

TGC CCC TTT CCA CTG GCT GAC CAC CTC AAC TCA ACC AAC CAT GCC ATT     1470
Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr Asn His Ala Ile
                345                 350                 355

GTG CAG ACC CTG GTC AAT TCT GTC AAT TCC AGT ATC CCC AAA GCC TGT     1518
Val Gln Thr Leu Val Asn Ser Val Asn Ser Ser Ile Pro Lys Ala Cys
            360                 365                 370
```

```
TGT GTG CCC ACT GAA CTG AGT GCC ATC TCC ATG CTG TAC CTG GAT GAG      1566
Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu
        375                 380                 385

TAT GAT AAG GTG GTA CTG AAA AAT TAT CAG GAG ATG GTA GTA GAG GGA      1614
Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu Gly
    390                 395                 400

TGT GGG TGC CGC TGAGATCAGG CAGTCCTTGA GGATAGACAG ATATACACAC          1666
Cys Gly Cys Arg
405

ACACACACAC ACACCACATA CACCACACAC ACACGTTCCC ATCCACTCAC CCACACACTA     1726

CACAGACTGC TTCCTTATAG CTGGACTTTT ATTTAAAAAA AAAAAAAAAA AAACCCGAAT    1786

TC                                                                   1788
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 408 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Met Ile Pro Gly Asn Arg Met Leu Met Val Val Leu Leu Cys Gln Val
 1               5                  10                  15

Leu Leu Gly Gly Ala Ser His Ala Ser Leu Ile Pro Glu Thr Gly Lys
            20                  25                  30

Lys Lys Val Ala Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly
        35                  40                  45

Gln Ser His Glu Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met
    50                  55                  60

Phe Gly Leu Arg Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro
65                  70                  75                  80

Asp Tyr Met Arg Asp Leu Tyr Arg Leu Gln Ser Gly Glu Glu Glu Glu
                85                  90                  95

Glu Gln Ile His Ser Thr Gly Leu Glu Tyr Pro Glu Arg Pro Ala Ser
            100                 105                 110

Arg Ala Asn Thr Val Arg Ser Phe His His Glu Glu His Leu Glu Asn
        115                 120                 125
```

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Ile Pro Gly Thr Ser Glu Asn Ser Ala Phe Arg Phe Leu Phe Asn Leu
    130                 135                 140

Ser Ser Ile Pro Glu Asn Glu Val Ile Ser Ser Ala Glu Leu Arg Leu
145                 150                 155                 160

Phe Arg Glu Gln Val Asp Gln Gly Pro Asp Trp Glu Arg Gly Phe His
                165                 170                 175

Arg Ile Asn Ile Tyr Glu Val Met Lys Pro Pro Ala Glu Val Val Pro
            180                 185                 190

Gly His Leu Ile Thr Arg Leu Leu Asp Thr Arg Leu Val His His Asn
        195                 200                 205

Val Thr Arg Trp Glu Thr Phe Asp Val Ser Pro Ala Val Leu Arg Trp
    210                 215                 220

Thr Arg Glu Lys Gln Pro Asn Tyr Gly Leu Ala Ile Glu Val Thr His
225                 230                 235                 240

Leu His Gln Thr Arg Thr His Gln Gly Gln His Val Arg Ile Ser Arg
                245                 250                 255

Ser Leu Pro Gln Gly Ser Gly Asn Trp Ala Gln Leu Arg Pro Leu Leu
            260                 265                 270

Val Thr Phe Gly His Asp Gly Arg Gly His Ala Leu Thr Arg Arg Arg
        275                 280                 285

Arg Ala Lys Arg Ser Pro Lys His His Ser Gln Arg Ala Arg Lys Lys
    290                 295                 300

Asn Lys Asn Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val
305                 310                 315                 320

Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr
                325                 330                 335

Cys His Gly Asp Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr
            340                 345                 350

Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Ser Ile
        355                 360                 365

Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu
    370                 375                 380

Tyr Leu Asp Glu Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met
385                 390                 395                 400
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Val Val Glu Gly Cys Gly Cys Arg
405

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..102
(D) OTHER INFORMATION: /note= "BMP5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
1 5 10 15

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly
20 25 30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
35 40 45

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys
50 55 60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65 70 75 80

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
85 90 95

Arg Ser Cys Gly Cys His
100

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..102
(D) OTHER INFORMATION: /note= "BMP6"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Cys Arg Lys His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Gln
1               5                  10                  15

Asp Trp Ile Ile Ala Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly
            20                  25                  30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
        35                  40                  45

Ile Val Gln Thr Leu Val His Leu Met Asn Pro Glu Tyr Val Pro Lys
    50                  55                  60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65                  70                  75                  80

Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Trp Met Val Val
                85                  90                  95

Arg Ala Cys Gly Cys His
            100
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..102
(D) OTHER INFORMATION: /label= OPX
/note= "WHEREIN XAA AT EACH POS'N IS INDEPENDENTLY SELECTED FROM THE RESIDUES OCCURRING AT THE CORRESPONDING POS'N IN THE C-TERMINAL SEQUENCE OF MOUSE OR HUMAN OP1 OR OP2 (SEE SEQ. ID NOS. 1,8,10 AND 12.)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Xaa Xaa His Glu Leu Tyr Val Xaa Phe Xaa Asp Leu Gly Trp Xaa
1 5 10 15

Asp Trp Xaa Ile Ala Pro Xaa Gly Tyr Xaa Ala Tyr Tyr Cys Glu Gly
20 25 30

Glu Cys Xaa Phe Pro Leu Xaa Ser Xaa Met Asn Ala Thr Asn His Ala
35 40 45

Ile Xaa Gln Xaa Leu Val His Xaa Xaa Xaa Pro Xaa Xaa Val Pro Lys
50 55 60

Xaa Cys Cys Ala Pro Thr Xaa Leu Xaa Ala Xaa Ser Val Leu Tyr Xaa
65 70 75 80

Asp Xaa Ser Xaa Asn Val Xaa Leu Xaa Lys Xaa Arg Asn Met Val Val
85 90 95

Xaa Ala Cys Gly Cys His
100

What is claimed is:

1. A method for promoting in vivo osseointegration of an implantable, prosthetic device, the method comprising the steps of:

providing on a surface of the prosthetic device substantially pure osteogenic protein, and

implanting the device in a mammal at a site wherein bone tissue and said surface are maintained at least partially in contact for a time sufficient to permit enhanced bone tissue growth between said tissue and said device.

2. In the method of repairing the skeletal system of a mammal comprising surgically implanting in contact with bone tissue a prosthetic device, and permitting the device and the bone tissue to integrate to form a weight bearing skeletal component, the improvement comprising:

providing substantially pure osteogenic protein on a surface of said device prior to its implantation thereby to promote enhanced bone tissue growth into said device and to improve the tensile strength of the junction between the bone and said device.

3. The method of claim 1 or 2 wherein said surface of said prosthetic device further comprises hydroxylapatite, collagen, homopolymers or copolymers of glycolic acid, lactic acid or butyric acid and derivatives thereof, tricalcium phosphate or other calcium phosphate, metal oxides or combinations thereof.

4. The method of claims 1 or 2 wherein the prosthetic device comprises a porous, metallic material.

5. The method of claim 1 or 2 wherein the osteogenic protein is an osteogenically active dimeric protein.

6. The method of claim 1 or 2 wherein the osteogenic protein is an osteogenically active dimeric protein produced by expression of recombinant DNA in a host cell, and comprises a pair of polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence comprising residues 335 to 431 of Seq. ID No. 1 (OPS) such that said pair of polypeptide chains, when disulfide bonded to produce a dimeric species, has a conformation capable of inducing endochondral bone formation in association with said surface when implanted in a mammal.

7. The method of claim 1 or 2 wherein the osteogenic protein is an osteogenically active dimeric protein expressed from recombinant DNA in a host cell, characterized in that the protein comprises a pair of oxidized subunits disulfide bonded to produce a dimeric species, one of said subunits having an amino acid sequence encoded by a nucleic acid capable of hybridizing to a nucleic acid encoding OPS (residues 335 to 431 of Seq. ID No. 1) under stringent hybridization conditions, such that the disulfide bonded dimeric species comprising said subunit has a conformation capable of inducing endochondral bone formation in a mammal when disposed on the surface of said device.

8. The method of claim 1 or 2 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that one of the chains of said protein comprises an amino acid sequence sharing greater than 60% identity with an amino acid sequence comprising residues 335 to 431 of Seq. ID No. 1 (OPS).

9. The method of claim 8 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that the amino acid sequence of said chain of said protein comprises an amino acid sequence sharing greater than 65% identity with an amino acid sequence comprising OPS.

10. The method of claim 9 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that the amino acid sequence of said chain of said protein comprises residues 335-431 of Seq. ID No. 1 (OPS).

11. The method of claim 9 wherein the osteogenic protein is an osteogenically active dimeric protein which is a homodimer, wherein both chains comprise the amino acid sequence of OPS (residues 335-431 of Seq. ID No.1.)

12. The method of claim 11 wherein both chains of said osteogenically active dimeric protein comprise the amino acid sequence of residues 293-431 of Seq. ID No. 1 (OP1-18Ser.)

13. An improved prosthetic device for repairing mammalian skeletal defects, injuries, or anomalies comprising a rigid prosthetic implant having a porous or non-porous surface region for implantation adjacent bone tissue, wherein the improvement comprises:

substantially pure osteogenically active osteogenic protein disposed on said surface region in an amount sufficient to promote enhanced bone tissue growth into said surface.

14. The device of claim 13 wherein said surface of said prosthetic device further comprises hydroxylapatite.

15. The device claim 13 wherein the osteogenic protein is an osteogenically active dimeric protein.

16. The device of claim 13 wherein the osteogenic protein is an osteogenically active dimeric protein produced by expression of recombinant DNA in a host cell, and comprises a pair of polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence comprising residues 335-431 of Seq. ID No.1 (OPS), such that said pair of polypeptide chains, when disulfide bonded to produce a dimeric species, has a conformation capable of inducing endochondral bone formation in association with said surface when implanted in a mammal.

17. The device of claim 13 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that the protein comprises a pair of oxidized subunits disulfide bonded to produce a dimeric species, one of said subunits having an amino acid sequence encoded by a nucleic acid capable of hybridizing to a nucleic acid encoding OPS (residues 335-431 of Seq. ID No. 1), such that the disulfide bonded dimeric species comprising said subunit has a conformation capable of inducing endochondral bone formation in a mammal when disposed on the surface of said device.

18. The device of claim 13 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that one of the chains of said protein comprises an amino acid sequence sharing greater than 65% identity with an amino acid sequence comprising OPS (residues 335 to 431 of Seq. ID No. 1).

19. The device of claim 18 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that the amino acid sequence of said chain of said protein comprises an amino acid sequence sharing greater than 65% identity with an amino acid sequence comprising OPS (residues 335-431 of Seq. ID No. 1).

20. The device of claim 19 wherein the osteogenic protein is an osteogenically active dimeric protein characterized in that the amino acid sequence of said chain of said protein comprises residues 335-431 of Seq. ID No. 1 (OPS).

21. The device of claim 19 wherein the osteogenic protein is an osteogenically active dimeric protein which is a homodimer, wherein both chains comprise the amino acid sequence of OPS (residues 335-431 of Seq. ID No. 1).

22. The device of claim 21 wherein wherein both chains of said osteogenically active dimeric protein comprise the amino acid sequence of residues 293-431 of Seq. ID No.1 (OP1-18Ser.)

23. The device of claim 13 wherein the prosthesis comprises a porous metallic material.

24. The device of claim 13 wherein the prosthesis comprises a contoured implantable portion for insertion into an orifice having plural indentations transverse to its longitudinal axis.

25. The device of claim 24 comprising a dental implant.

26. A method for promoting in vivo osseointegration of a prosthetic device into an orifice of a bone, comprising the steps of:

providing a prosthetic device having a contoured implantable portion for insertion into said orifice, said contoured portion having plural indentations transverse to its longitudinal axis, and

implanting into the orifice the contoured portion of the prosthetic device and a bone growth composition comprising a substantially pure osteogenic protein combined with a matrix material which induces bone growth in said indentations, osseointegration between the bone and the prosthetic device, and osseointegration of new bone induced by said composition and said bone.

27. The method of claim 26 wherein the contoured portion comprises a porous metallic material.

28. The method of claim 27 wherein the osteogenic protein enhances bone ingrowth into said pores.

29. A device for promoting in vivo osseointegration of a prosthesis into an orifice of a bone, comprising

a rigid prosthetic implant having a contoured portion for insertion into said orifice, said contoured portion having plural indentations transverse to its longitudinal axis, and

a bone growth composition comprising a substantially pure osteogenic protein combined with a matrix material which induces bone growth in said indentations, osseointegration between the bone and the prosthetic implant and osseointegration of new bone induced by said composition and said bone.

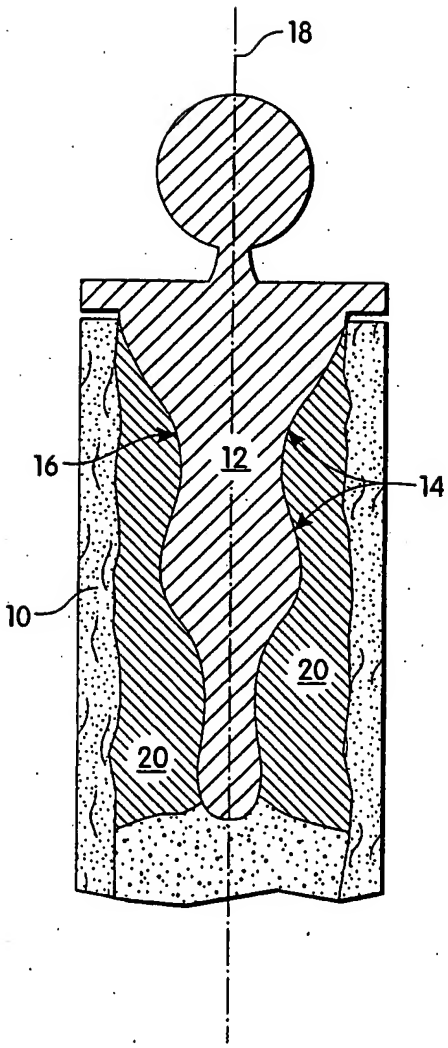
30. The device of claim 29 wherein the contoured portion comprises a porous metallic material.

31. The device of claim 30 wherein the osteogenic protein enhances bone ingrowth into said pores.

32. The device of claim 29 wherein said matrix material is selected from the group consisting of hydroxylapatite, collagen, polymers or copolymers of glycolic acid, lactic acid or butyric acid, tricalcium phosphate or other calcium phosphates, metal oxides, demineralized guanidine extracted bone and combinations thereof.

33. The device of claim 29 comprising a dental implant.

34. The device of claim 29 wherein the osteogenic protein is an osteogenically active dimeric protein produced by expression of recombinant DNA in a host cell, and comprises a pair of polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence comprising residues 335 to 431 of Seq. ID No. 1 (OPS) such that said pair of polypeptide chains, when disulfide bonded to produce a dimeric species, has a conformation capable of inducing endochondral bone formation in association with said contoured portion of said prosthesis when implanted in a mammal.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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/05446

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L27/00; A61K37/02; A61K6/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61L ; A61K ; C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,8 800 205 (GENETICS INSTITUTE) 14 January 1988 cited in the application	13,14,23
Y	see page 9, line 1 - line 2; claims 1,2,7 see abstract	15-22, 24,25, 29-34
X	EP,A,0 361 896 (COLLAGEN CORPORATION) 4 April 1990	13,14,23
Y	see column 5, line 28 - line 53 see column 7, line 19 - line 26; claims 1,3-7,16,19	30-32
X	EP,A,0 182 483 (COLLAGEN CORPORATION) 28 May 1986 see page 13, line 12 - line 19 see page 5, line 1 - line 3; claims 1,3,7	13,14,23

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 OCTOBER 1993	28. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	PELTRE CHR.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO,A,9 105 802 (CREATIVE BIOMOLECULES) 2 May 1991 cited in the application see page 69 - page 70 see page 3, line 1 - line 3	15-22,34
Y	EP,A,0 106 946 (SULZER) 2 May 1984 see figure 3	24,29
Y	DE,A,2 534 593 (LUKESCH F.) 26 February 1976 see claim 1; figure 1	24,25, 29,33
A	EP,A,0 470 305 (OSTEOTECH) 12 February 1992	
A	EP,A,0 413 492 (OSTEOTECH) 20 February 1991	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/05446

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-12,26-28 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9305446
SA 76365

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 14/10/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8800205	14-01-88	US-A-	4877864	31-10-89
		AU-B-	613314	01-08-91
		AU-A-	7783587	29-01-88
		EP-A-	0313578	03-05-89
		JP-T-	2500241	01-02-90
		US-A-	5013649	07-05-91
		US-A-	5166058	24-11-92
		US-A-	5187076	16-02-93
		US-A-	5116738	26-05-92
		US-A-	5106748	21-04-92
		US-A-	5108922	28-04-92
		US-A-	5141905	25-08-92
EP-A-0361896	04-04-90	US-A-	5108436	28-04-92
		AU-B-	628083	10-09-92
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		JP-A-	2218372	31-08-90
		US-A-	5207710	04-05-93
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		AU-B-	585268	15-06-89
		AU-A-	4900585	01-05-86
		CA-A-	1266613	13-03-90
		JP-A-	62016421	24-01-87
		US-A-	4888366	19-12-89
		US-A-	5001169	19-03-91
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		AU-A-	6648190	16-05-91
		CA-A-	2042577	18-04-91
		EP-A-	0448704	02-10-91
		JP-T-	4502336	23-04-92
		CA-A-	2027259	18-04-91
EP-A-0106946	02-05-84	CH-A-	657266	29-08-86
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		AU-A-	8389175	17-02-77
		CH-A-	603147	15-08-78
		JP-C-	985878	07-02-80

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9305446
SA 76365

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

14/10/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2534593		JP-A- 51041293	07-04-76
		JP-B- 54019118	12-07-79
		US-A- 3991472	16-11-76
EP-A-0470305	12-02-92	None	
EP-A-0413492	20-02-91	US-A- 5061286	29-10-91
		JP-A- 3178665	02-08-91